



NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-world treatment patterns and clinical outcomes for patients with relapsed/refractory multiple myeloma (RRMM) who received Elranatamab
Protocol number	C1071050
Protocol version identifier	2.0
Date	29 Apr 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000852
Active substance	L01FX32
Medicinal product	ELREXFIO™ (Elranatamab)
Research question and objectives	Research question: Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates (rwORR), real-world progression free survival (rwPFS), real world overall survival (rwOS), and the incidence of real-world AEs (as well as their treatment and related outcomes)? Primary objectives: In patients with RRMM treated with Elra in real-world clinical practice: • Describe real-world baseline demographic and clinical characteristics. • Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra- containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT). • Assess rwORR, rwPFS, and rwOS to Elra treatment. • Examine the incidence and treatment of and outcomes (dose or schedule change, therapy hold, therapy discontinuation, hospitalization) related to the following AEs: ○ ICANS ○ CRS ○ Peripheral Neuropathy ■ Peripheral neuropathy

	■ Sensory neuropathy ■ Motor neuropathy ○ Bacterial Infection ■ Sepsis ■ Bacteremia ■ Pneumonia (if documented as bacterial) ○ Viral Infection (non-COVID) ■ Adenovirus ■ Influenza ■ Rhinovirus ■ Hepatitis B Virus (acute or reactivation) ○ Lower Respiratory Infections (LRI) ■ Pneumonia ■ Pneumonitis (with infectious component) ■ Bronchiolitis ■ Tracheitis ○ Overall Infections (OI) ○ Hypogammaglobulinemia ■ Hypogammaglobulinemia ■ Low Immunoglobulin (Ig) G ■ Low IgA ■ Low IgM ■ Low IgE ■ Low IgD • Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved) Secondary Objectives To describe real-world patient characteristics, treatment patterns, rwORR, rwPFS, rwOS, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics: • Presence of extramedullary disease • High cytogenetic risk • Renal impairment (<i>depending on sample size</i>) • Elderly population (over 81)
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	- Setting of care for Elra step-up dose administration (inpatient vs. outpatient) Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes: - Severity of AEs that develop or worsen on or after the start of treatment with Elra - Safety grade of 2 and above and safety grade <2 (<i>only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra</i>) - CRS and ICANS by setting of care for Elra step-up dose administration
Country(ies) of study	United States of America
Author	Redacted [REDACTED] [REDACTED] [REDACTED]
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First line of therapy
5L	Fifth line of therapy
AE	Adverse Event
BCMA	B-cell maturation antigen
BMI	Body mass index
CAR-T	Chimeric Antigen Receptor T-cell therapy
CCI	Charlson comorbidity index
CGS	Consensus Genomic Staging
CI	Confidence interval
CR	Complete response
CRS	Cytokine release syndrome
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic health record
Elra	Elranatamab
ETL	Extract, Transform, and Load
FDA	U.S. Food and Drug Administration
Redacted	
FISH	Fluorescence In Situ Hybridization
FLC	Free light chain
GFR	Glomerular filtration rate
GPP	Good Publication Practice
HMA-EMA	Heads of Medicines Agencies–European Medicines Agency

ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
IFEM	International Federation of Emergency Medicine
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMS	International Myeloma System
IMWG	International Myeloma Working Group
IQR	Interquartile range
IRB	Institutional Review Board
ISS	International Staging System
IVIG	Intravenous immunoglobulin
KM	Kaplan–Meier
KOL	Key Opinion Leader
LCMM	Light chain multiple myeloma
LOINC	Logical Observation Identifiers, Names, and Codes
LOT	Line of therapy
LRI	Lower respiratory infections
mAbs	Monoclonal antibodies
ML	Machine learning
MM	Multiple Myeloma
mSMART	Mayo Stratification for Myeloma and Risk-Adapted Therapy
NCCN	National Comprehensive Cancer Network

NFK	National Kidney Foundation
NIS	Non-interventional study
NLP	Natural language processing
NT	Neurotoxicity
OI	Overall infections
PHI	Protected Health Information
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks (biweekly dosing)
QA	Quality assurance
QC	Quality control
RI	Renal impairment
RRMM	Relapsed/refractory multiple myeloma
RWD	Real-world data
RWE	Real-world evidence
rwAE	Real-world adverse event
rwORR	Real-world overall response rate
rwOS	Real-world overall survival
rwPFS	Real-world progression-free survival
SCT	Stem cell transplant
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic status
SSDI	Social Security Death Index
SPEP	Serum protein electrophoresis

SQL	Structured Query Language
UPEP	Urine protein electrophoresis
USA	United States of America

2. RESPONSIBLE PARTIES

[illegible]

3. ABSTRACT

Title: Real-world treatment patterns and clinical outcomes for patients with relapsed/refractory multiple myeloma (RRMM) who received elranatamab

Version: 1.0

Date: 29 April 2026

Authors: Redacted.

Rationale and background: Elranatamab (Elra), a bispecific antibody that targets B-cell maturation antigen (BCMA), received accelerated approval by the U.S. Food and Drug Administration (FDA) in 2023 for the treatment of adult patients with RRMM who have received at least four prior lines of therapy. Although clinical trials provide critical efficacy and safety data, real-world evidence (RWE) is needed to understand treatment patterns, effectiveness, and safety outcomes in broader patient populations outside controlled trial settings. This study aims to fill this evidence gap by comprehensively characterizing the treatment patterns, real-world overall response rate (rwORR), real-world progression free survival (rwPFS), real-world overall survival (rwOS), and adverse events (AEs) among RRMM patients treated with Elra.

Research question and objectives: Among patients with RRMM treated with Elranatamab in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, real-world response rates (rwORR), real-world progression free survival (rwPFS), real-world overall survival (rwOS), incidence of real-world Adverse Events (rwAEs), treatment and related outcomes?

Research question:

Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates (rwORR), rwPFS, rwOS, and the incidence of real-world AEs (as well as their treatment and related outcomes)?

Primary objectives:

In patients with RRMM treated with Elra in real-world clinical practice:

- Describe real-world baseline demographic and clinical characteristics.
- Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra-containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT).
- Assess rwORR, rwPFs, and rwOS to Elra treatment.
- Examine the incidence and treatment of and outcomes (dose or schedule change, therapy hold, therapy discontinuation, hospitalization) related to the following AEs:
 - ICANS
 - CRS
 - Peripheral Neuropathy
 - Peripheral neuropathy
 - Sensory neuropathy
 - Motor neuropathy

- Bacterial Infection
 - Sepsis
 - Bacteremia
 - Pneumonia (if documented as bacterial)
- Viral Infection (non-COVID)
 - Adenovirus
 - Influenza
 - Rhinovirus
 - Hepatitis B Virus (acute or reactivation)
- Lower Respiratory Infections (LRI)
 - Pneumonia
 - Pneumonitis (with infectious component)
 - Bronchiolitis
 - Tracheitis
- Overall Infections (OI)
- Hypogammaglobulinemia
 - Hypogammaglobulinemia
 - Low Immunoglobulin (Ig) G
 - Low IgA
 - Low IgM
 - Low IgE
 - Low IgD
- Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved)

Secondary Objectives

To describe real-world patient characteristics, treatment patterns, rwORR, rwPFS, rwOS, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics:

- Presence of extramedullary disease
- High cytogenetic risk
- Renal impairment (*depending on sample size*)
- Elderly population (over 81)
- Setting of care for Elra step-up dose administration (inpatient vs. outpatient)

Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes:

- Severity of AEs that develop or worsen on or after the start of treatment with Elra
- Safety grade of 2 and above and safety grade <2 (*only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra*)
- CRS and ICANS by setting of care for Elra step-up dose administration

Study design: This is a retrospective, observational cohort study using de-identified electronic health record (EHR)-derived data from the [Redacted]. The study will evaluate real-world patient characteristics, treatment patterns, rwORR, rwOS, rwPFS, and AEs among RRMM patients treated with Elra and in specific sub-populations of interest.

Study Population: US patients diagnosed with MM on or after January 1, 2013, who received Elra treatment. This study will be conducted using the [Redacted]. The database includes data from a large, demographically and geographically diverse network of oncology practices across the United States, encompassing both community oncology clinics and academic medical centers.

Study Outcomes Variables: Real-world overall response rate (rwORR), real-world progression free survival (rwPFS), real-world overall survival (rwOS), incidence and treatment of AEs, and outcomes related to AEs (dose or schedule change, therapy hold, therapy discontinuation, hospitalization). These will be reported for the overall cohort and subgroups based on baseline characteristics (presence of extramedullary disease, high cytogenetic risk, performance status, renal impairment [*if sample size allows*], age [81 years of age and older], and setting of care for Elra step-up dose administration (inpatient vs. outpatient). Baseline characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes: severity of AEs that occur during the follow-up period, as well as safety grade 2 and above, and safety grade <2 [*only available for immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS)*], and CRS and ICANS by setting of care for Elra step-up dose administration.

Data Source(s): The [Redacted] is a longitudinal database derived from EHRs from cancer care providers across the United States.

Study Size: Approximately 120 patients

Data Analysis: Descriptive statistics will be used to summarize demographics, clinical characteristics, treatment patterns, incidence of AEs, and rwORR. Kaplan-Meier (KM) time-to-event analysis will be used for rwPFS and rwOS. For continuous variables, the descriptive statistics will include medians, interquartile range (IQR), means, standard deviations, and minimum and maximum values (as applicable). For categorical variables, frequencies, and percentages will be generated. The number of patients with missing data will be reported for all variables. Levels of categorical variables may be combined to account for small sample sizes. Analyses will be primarily descriptive.

Milestones:

Milestone	Planned Date
Start date of data collection	30-Jan-2026
End date of data collection	02-Feb-2026
Registration in the HMA-EMA Catalogues of RWD Studies	29-Jan-2026
Final Study Report	01-Feb-2027

4. AMENDMENTS AND UPDATES

Versi on Ident ifier	Date	Amend ment Type (substa ntial or admini strative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	22-May-2026	Substan tial	Addition of rwPFS and rwOS to Section 7. Research Question and Objectives ; Section 8.7.2 Primary Analyses; Section 3. Abstract; Section 8.9 Strengths and Limitations of the Research Methods	Addition of rwPFS and rwOS effectiveness outcome endpoints	Since study initiation, sufficient follow-up has accrued (median follow-up >12 months). Based on this data maturity, the EvGen subcommittee agreed that it was appropriate to expand the protocol to include time-to-event outcomes, including rwPFS and rwOS.
2.0	22-May-2026	Substan tial	Addition of Prophylactic IVIG to Section 8.3 Variables (Table 1. Study Variables); Section 8.9 Strengths and Limitations of the Research Methods	Addition of study variable Prophylactic IVIG	Feedback from key opinion leaders (KOLs) indicated that documenting prophylactic IVIG use would help contextualize observed infection rates in the elranatamab-treated cohort, particularly if lower-than-expected infection incidence is observed.
2.0	22-May-2026	Substan tial	Cohort wording updates to Section 8.3. Variables (Table 1. Study Variables); Section 8.9 Strengths and Limitations of	Cohort wording updates to distinguish ICANS from Neurotoxicity (NT)	ICANS is a distinct and well-defined clinical syndrome. Separating ICANS from broader neurotoxicity terminology improves clinical specificity,

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			the Research Methods		and reduces potential misclassification.
2.0	22-May-2026	Substantial	Inclusion of language in the annex (ANNEX 3. Additional Information Section) regarding progression and mortality capture and definitions	Inclusion of language regarding progression and mortality capture and definitions	Additional detail was added to clarify how progression and mortality are captured within Redacted data, including data sources and operational definitions, to improve transparency and interpretability of rwPFS and rwOS analyses for this cohort.
2.0	22-May-2026	Administrative	Formatting update to ANNEX 3. Additional Information Section to introduce numbered headers for each subsection	Numbered headings were added to all subsections within ANNEX 3 – Additional Information Section to improve structure, clarity, and ease of navigation.	To enhance readability and provide a more organized presentation of the ANNEX 3 section.

5. MILESTONES

Milestone	Planned Date
Start date of data collection	30-Jan-2026
End date of data collection	02-Feb-2026
Registration in the HMA-EMA Catalogues of RWD Studies	29-Jan-2026
Final Study Report	01-Feb-2027

6. RATIONALE AND BACKGROUND

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells, monoclonal protein production, and progressive end-organ damage [1]. MM accounts for approximately 1–2% of all cancers and ~10% of hematologic malignancies worldwide, with an estimated 35,000 new cases annually in the United States [2,3]. Despite advances in therapeutic options over the past two decades, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies, MM remains largely incurable, and most patients eventually relapse [4].

Patients with RRMM who are triple-class exposed or refractory to PI, IMiD, and anti-CD38 antibodies face poor outcomes, with median progression-free survival (PFS) often less than 6 months and overall survival (OS) typically less than 1 year [5,6]. This underscores the critical need for novel therapies with distinct mechanisms of action in later-line settings.

Elranatamab (Elra) is a bispecific antibody that targets B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, redirecting T-cell cytotoxicity against malignant plasma cells [7]. Clinical trials, including the pivotal phase 2 MagnetisMM-3 study, have demonstrated that Elra induces deep and durable responses in heavily pretreated RRMM patients, with an overall response rate (ORR) of ~60% and manageable toxicity profile [8]. The most common AEs include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are typically low-grade and manageable with appropriate mitigation strategies [9].

Based on these results, elranatamab received accelerated approval from the U.S. Food and Drug Administration (FDA) on 14 August 2023 for the treatment of adult patients with RRMM who have received at least four prior lines of therapy, including a PI, an IMiD, and an anti-CD38 antibody [10]. While pivotal clinical trials provide critical efficacy and safety data, real-world evidence (RWE) is needed to understand treatment patterns, effectiveness, and safety outcomes in broader patient populations outside of controlled trial settings. In particular, RWE can help characterize:

- Patient characteristics and prior treatment histories of Elra users;
- Patterns of Elra initiation and sequencing in routine clinical practice;
- Real-world effectiveness, including response, progression-free, and overall survival;
- Safety outcomes, including incidence and management of CRS, ICANS, infections, cytopenias, and other AEs in diverse clinical settings.

Recently, in real-world settings, compassionate use programs and retrospective studies have provided additional insights. Malard et al. reported that in a French compassionate use study of Elra in RRMM (n=101), the ORR was 51.5%, with efficacy and safety largely consistent with the MagnetisMM-3 trial. CRS (45%, all grade 1–2) and infections (49% overall; 24% grade ≥3) were the most common toxicities, emphasizing the importance of proactive safety monitoring in clinical practice [11]. Similarly, a retrospective analysis at Moffitt Cancer Center confirmed encouraging outcomes in heavily pretreated RRMM patients treated with Elra, showing clinically meaningful responses and durable benefit with an ORR consistent with trial data, though rates of treatment modifications due to AEs were higher in real-world practice [12]. Such real-world analyses provide valuable context for treatment effectiveness and tolerability in routine practice. However, real-world data (RWD) on Elra remain limited, particularly with respect to detailed safety outcomes, consistency of real-world overall response rate (rwORR), and longer-term real-world effectiveness outcomes, including real-world progression-free survival (rwPFS) and real-world overall survival (rwOS), across diverse clinical practice settings. This study aims to address this evidence gap by systematically evaluating real-world treatment patterns, rwORR, rwPFS, rwOS, and safety outcomes of Elra, complementing clinical trial findings. Findings from this study will provide important insights to clinicians, patients,

and regulators regarding the real-world effectiveness, safety, and role of Elra in the treatment of RRMM.

This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Research question:

Among patients with RRMM treated with Elra in a real-world setting, what are the demographic and clinical characteristics, treatment patterns, response rates, rwPFS, rwOS, and the incidence of real-world AEs (as well as their treatment and related outcomes)?

Primary objectives:

In patients with RRMM treated with Elra in real-world clinical practice:

- Describe real-world baseline demographic and clinical characteristics.
- Describe treatment patterns in all lines of therapy prior to receipt of Elra, during the Elra-containing line of therapy (LOT), and of the first subsequent LOT following the Elra-containing LOT (for those who have a subsequent LOT).
- Assess rwORR, rwPFS, rwOS to Elra treatment.
- Examine the incidence and treatment of and outcomes (dose or schedule change, therapy hold, therapy discontinuation, hospitalization) related to the following AEs:
 - ICANS
 - CRS
 - Peripheral Neuropathy
 - Peripheral neuropathy
 - Sensory neuropathy
 - Motor neuropathy
 - Bacterial Infection
 - Sepsis
 - Bacteremia
 - Pneumonia (if documented as bacterial)
 - Viral Infection (non-COVID)
 - Adenovirus
 - Influenza
 - Rhinovirus
 - Hepatitis B Virus (acute or reactivation)
 - Lower Respiratory Infections (LRI)
 - Pneumonia
 - Pneumonitis (with infectious component)
 - Bronchiolitis

- Tracheitis
- Overall Infections (OI)
- Hypogammaglobulinemia
 - Hypogammaglobulinemia
 - Low Immunoglobulin (Ig) G
 - Low IgA
 - Low IgM
 - Low IgE
 - Low IgD
- Time from first administration of Elra to onset or worsening of baseline real-world adverse events (rwAEs) will be estimated, as well as resolution status and time to resolution (for those that were noted to be resolved)

Secondary Objectives

To describe real-world patient characteristics, treatment patterns, ORR, rwPFS, rwOS, and AEs among RRMM patients treated with Elra in the following subgroups of interest, based on baseline characteristics:

- Presence of extramedullary disease
- High cytogenetic risk
- Renal impairment (*depending on sample size*)
- Elderly population (over 81)
- Setting of care for Elra step-up dose administration (inpatient vs. outpatient)

Patient characteristics and treatment patterns will also be reported by the following groupings, which are conditional and based on outcomes:

- Severity of AEs that develop or worsen on or after the start of treatment with Elra
- Safety grade of 2 and above and safety grade <2 (*only available for ICANS and CRS that develops or worsens on or after the start of treatment with Elra*)
- CRS and ICANS by setting of care for Elra step-up dose administration

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective, observational cohort study of patients with RRMM using the Redacted de-identified electronic health record (EHR)-derived database. The dataset generated for the study will include all protocol-required, retrospective patient-level data available for eligible patients within the study period. This retrospective cohort design was chosen to leverage existing EHR data, enabling comprehensive assessment of real-world treatment patterns and clinical and safety outcomes in a diverse RRMM population of patients treated with Elra and provides insights into routine clinical practice across diverse settings, which may not be fully represented in clinical trials. No formal comparison group is included, as the study aims to describe outcomes in Elra treated patients. The primary endpoints are the rwORR, rwPFS, and rwOS to Elra as well as the incidence and management of adverse events as outlined in the primary objectives. Secondary endpoints are

subgroup analyses describing real-world patient characteristics, treatment patterns, overall response rate (rwORR), rwPFS, rwOS, and adverse events (AEs) among RRMM patients treated with Elranatamab, stratified by baseline factors such as extramedullary disease, cytogenetic risk, renal impairment, age, and setting of care. Additional subgroup analyses will report outcomes by severity and grade of AEs, and by setting of care for step-up dosing. All endpoints will be summarized using descriptive statistics (means, medians, IQRs). Analyses will be primarily descriptive.

Study Period

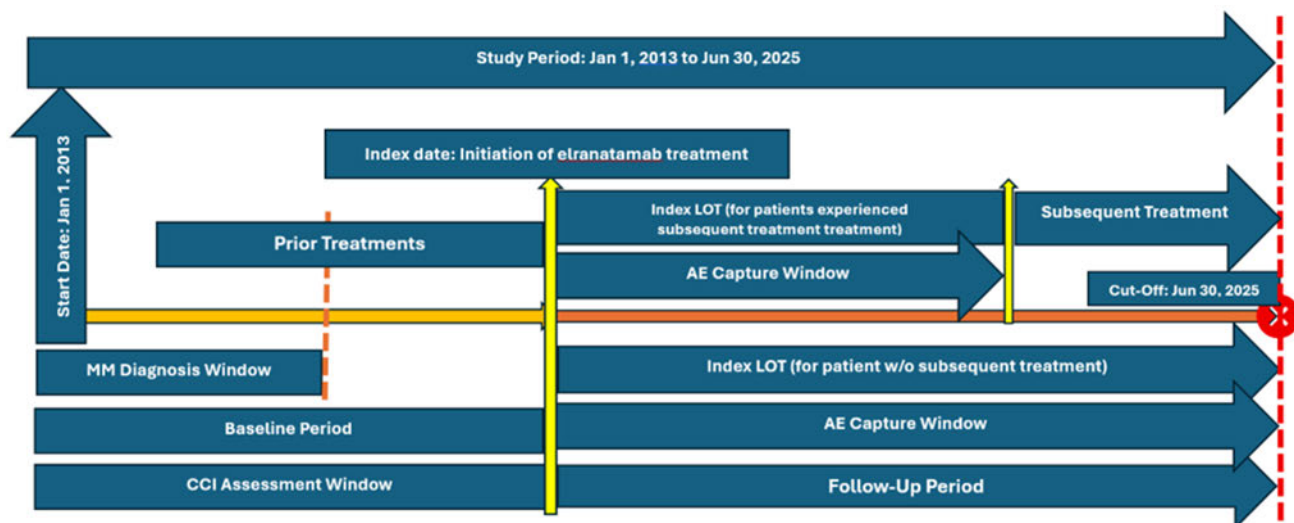
The study observation period will begin on January 01, 2013, and extend up to the data cutoff date of June 30, 2025. The index date will be defined as the date of the first documented administration of Elra on or after August 14, 2023 (date of FDA approval). Baseline characteristics will be assessed within the baseline window, generally defined as from the patient's date of initial diagnosis with multiple myeloma to index date with the closest measurement to index date being used. The follow-up period will be defined as the time from index date through the date of death, last confirmed activity, or data-cutoff, whichever occurs first.

Figure 1. below illustrates the overall study design. The study will describe the real-world treatment patterns and evaluate real-world outcomes among adult patients with RRMM who received Elra in routine clinical practice.

Figure 1. Study Design Scheme

This figure illustrates the study design, including key time windows and follow-up periods.

The index date refers to the date of initial treatment with elranatamab on or after 14 August 2023. The study period spans from 01 January 2013 (start date) to 30 June 2025 (data cutoff). The multiple myeloma (MM) diagnosis window extends from 01 January 2013 to the index date. The baseline period is from 01 January 2013 to the index date. The Charlson Comorbidity Index (CCI) assessment window will be evaluated prior to the index date; for patients with multiple CCI-related tests within the baseline period, the test value on or closest to the index date will be selected. Prior treatments include all therapies received after MM diagnosis and before the index date. Index LOT refers to the elranatamab-containing line of therapy corresponding to the index date. Patients will be followed from the index date to the earliest of death, last confirmed activity date (defined as a recording of vital information, medication administration, laboratory test/result being reported, or last abstracted therapy date), or data cutoff. The adverse event (AE) capture window spans from the index date to the earliest of death, last confirmed activity date, initiation of a new LOT, or data cutoff. Subsequent treatment refers to the first line of therapy after elranatamab treatment, if available.



8.2. Setting

This study will be conducted using the **Redacted** Research Database (**Redacted**). The database includes data from a large, demographically and geographically diverse network of oncology practices across the United States, encompassing both community oncology clinics and academic medical centers. **Redacted** data are sourced directly from routine clinical practice and include structured information (e.g., demographics, laboratory results, prescribing records) as well as unstructured data curated through technology-enabled abstraction of physician notes, pathology reports, and radiology reports. Data are longitudinal and refreshed monthly, enabling the capture of real-world treatment patterns, clinical outcomes, and safety events as they occur in practice. This setting reflects the routine clinical management of patients with relapsed/refractory multiple myeloma outside the controlled conditions of clinical trials, providing the opportunity to evaluate the use of Elra in a broader, more heterogeneous patient population.

Study population : Adult patients (aged 18 years and older) diagnosed with relapse/refractory multiple myeloma (RRMM) who received Elra treatment.

Place: Oncology practices participating in the **Redacted** network across the United States

Time Period: The study observation period begins on January 1, 2013, and extends up to the data cutoff date of June 30, 2025. The index date is defined as the date of the first documented administration of Elra on or after August 14, 2023 (the date of FDA approval).

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients included in **Redacted**
 - Has at least two documented clinical visits, on different days in the **Redacted** database on or after January 1, 2013
2. Has an International Classification of Diseases (ICD) diagnosis of MM using (ICD-9: 203.0x or ICD-10 C90.0x, C90)
3. Has evidence of treatment of Elra, on or after MM diagnosis and on or after 14 August 2023 (date of FDA approval)

4. Aged 18+ years as of first initiation of Elra
5. Prior to Elra initiation, has evidence of treatment with a proteasome inhibitor (bortezomib, carfilzomib, ixazomib), an IMiD (thalidomide, lenalidomide, pomalidomide), and an anti-CD38 (daratumumab, isatuximab)

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Lacking relevant unstructured documents in the **Redacted** database
2. Receipt of Elra in combination with any other agents
3. Receipt of clinical study drugs, indicating participation in a clinical study.

8.3. Variables

The variables listed below in Table 1 will be used to characterize patients' baseline information, clinical characteristics, real-world treatment patterns, and clinical outcomes. For baseline characteristics, values closest to the index date will be used unless otherwise noted. The full code can be found in [Annex 3](#).

Table 1. Study Variables

Outcome Variable	Role	Operational Definition	Assessment Period
Follow-up period	Outcome	Follow-up period is defined as length of time from the index date to the earliest of date of death, last confirmed activity date (defined as a recording of vital information, a medication administration, a laboratory test/result being reported or last abstracted therapy date), or data cutoff.	From index date to data cutoff date
rwORR - Partial response (PR) - Very good partial response (VGPR) or better	Outcome	rwORR will be defined as the proportion of patients who had at least one PR, VGPR, or better assessment, among patients with a baseline lab value and a subsequent lab value. PR and VGPR will be derived from enhanced M spike and free light chain (FLC) lab values based on IMWG criteria.	During Elra-containing LOT
rwPFS	Outcome	rwPFS is defined as time from index date to first real-world progression event after the index date, or date of death. Patients without a date of death or real-world progression event date are censored at their last clinic note date (or date of last confirmed structured activity if there is no clinic note) prior to the start of the subsequent LOT, or at their last available clinic note date if they do not have a subsequent LOT. Real-world progression events are defined as distinct instances when the treating clinician	From index date to data cutoff date during Elra containing LOT

		documents that there has been spread or worsening or growth of the tumor of interest.	
rwOS	Outcome	rwOS is defined as time from index date to date of death. Patients without a date of death are censored at their last confirmed EHR activity date.	From index date to data cutoff date
Safety Outcomes		Operational Definition	Assessment Period
Presence of rwAE at baseline	Baseline characteristic / Exposure	Number and proportion of patients who have evidence of the respective rwAE during the baseline period (defined here as 30 days prior to index LOT up to one day before index LOT)	30 days prior to the day before the index date
Incidence of new rwAEs during the index LOT	Outcome	The number and proportion of patients with evidence of first onset of the respective rwAE during the index LOT (first Elra-containing LOT) among the total number of patients in the cohort.	During Elra-containing LOT
Worsening of pre-existing rwAEs	Outcome	The number and proportion of patients with pre-existing rwAE (defined above as “presence of rwAE at baseline”) who experienced a worsening of the rwAE during the AE examination period divided by the total number of patients in the cohort will be reported. The AE is considered to worsen if: • The AE is present at baseline (ie, present within 30 days prior to index date) and is later documented to be worse/increased as compared to the status at baseline • The AE is present at baseline, resolves, and then recurs during the AE examination period	During Elra-containing LOT
Time to AE onset or worsening	Outcome	Time (in days) from index date to documented onset date of the rwAE or the initial worsening of baseline rwAE.	During Elra-containing LOT
AE-related outcome(s)	Outcome	Clinician-documented outcomes related to the selected rwAEs that occurred during the index LOT, as determined by abstraction, among patients with the selected AE, including: • Dose or schedule change - the dose was modified as a result of the rwAE or if the rwAE caused a change in treatment schedule (not a delay, but a change to the treatment schedule). • Therapy hold - the therapy of interest was held or delayed as a result of the rwAE. A therapy hold is defined as a temporary suspension of the planned dosing schedule.	During Elra-containing LOT

		• Therapy discontinuation - any component drug of the referenced treatment is discontinued (and not restarted) as a result of the rwAE. • Treatment for the AE - if any treatment (does not have to be pharmacological) is taken by the patient or recommended, prescribed, or administered by the clinician to treat the rwAE • Hospitalization - the patient was hospitalized during the time of or as a result of the rwAE • No outcome related to the AE - the AE did not result in any of the above therapy changes, additional treatment, or hospitalization Note: These categories are not mutually exclusive and more than one can be selected and reported.	
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Therapy attribution	Outcome	Level of attribution for the selected rwAE of interest as determined by the treating clinician, among patients with the selected AE: - Definite attribution - there is explicit clinician documentation that the rwAE is directly due to the referenced therapy (e.g., 'is due to treatment') - Likely attribution - there is explicit clinician documentation that the rwAE might be due to the referenced therapy (e.g., 'possibly related to drug') - Not attributed - there is explicit clinician documentation that the rwAE is not due to the referenced therapy or that the rwAE is due to another condition unrelated to reference therapy (e.g., 'not related to therapy') - No documentation - there is no explicit clinician documentation that the rwAE is or is not due to the referenced therapy (e.g., 'patient presents with significant viral infection - will hold therapy' without attribution of the viral infection is considered not documented)	During Elra-containing LOT
Clinician-documented severity	Outcome	Severity of the selected rwAE of interest as determined by the treating clinician, among patients with the selected AE: - Mild - Moderate - Severe - Life-threatening - Fatal - Not documented	During Elra-containing LOT

Resolution	Outcome	Clinician-documented resolution status of the selected rwAE of interest, among patients with the selected AE: - Resolved - The patient has recovered completely from the AE of interest; or the patient has returned to baseline status, for those with AE at baseline and there are no permanent impairments to the patient's health as a result of the AE of interest. - Resolving - The AE at the end of the LOT is reducing in grade or severity, or there is explicit documentation that the AE is "improving," "resolving," "marked improvement," "not as significant," or "getting better" - Resolved with sequelae - The patient has recovered from the AE of interest, but a permanent or long-standing impairment to the patient's health has resulted from the AE of interest. - Ongoing - The patient has not yet fully recovered from the AE of interest; or there is documentation that the AE is still occurring but not resolving at the end of the LOT; or there is documentation that the AE is the reason to discontinue therapy. - Fatal - There is clinician documentation that the patient expired directly as a result of the AE. - Not documented - There is no documented resolution of the AE.	During Elra-containing LOT
Time to resolution	Outcome	Time (in days) from rwAE start to date of resolution, for rwAEs marked as Resolved" or "Resolved with sequelae"	During Elra-containing LOT
CRS/ICANS	Outcome	- Clinician-reported grade of AE (available only for CRS/ICANS; note that the scales will not be standardized between clinicians) 1 2 3 4 5 - Not documented - ICANS will be captured among patients with neurotoxicity, with classification based on both clinical criteria and documentation. Patients	During Elra-containing LOT

		will be considered to have ICANS if they meet clinical criteria consistent with ICANS based on predefined terminology (see appendix), regardless of whether the term “ICANS” is explicitly documented. A supplemental variable will capture whether the term “ICANS” was explicitly documented in the medical record (yes/no).	
Tocilizumab Prophylaxis	Outcome	Prophylactic use of tocilizumab will be captured as a yes/no indicator, reflecting whether the patient received tocilizumab prior to elranatamab administration with prophylactic intent, as documented in the medical record. This is distinct from tocilizumab administered as treatment for an adverse event.	Prior to or at elranatamab initiation
IVIG Prophylaxis	Outcome	Prophylactic use of IVIG will be captured as a binary (yes/no) variable. “Yes” is defined as documented administration of IVIG within 60 days prior to, or around the time of, elranatamab initiation (e.g., step-up dosing or first treatment dose), with explicit or implicit clinician intent to prevent infection or manage hypogammaglobulinemia. This may include documentation in clinician notes, infusion records, or institutional protocols indicating prophylactic use. IVIG administered for treatment of active infection, for non-elranatamab-related indications, without documentation of prophylactic intent, or outside the defined time window without clear linkage to prophylaxis in this context will be classified as “No.”	Within 60 days prior to or around elranatamab initiation
Treatment for/Prevention of CRS/ICANS	Outcome	- Indication of Tocilizumab administration (Yes/No), date(s) of administration (MM/DD/YYYY, as available) - Indication of Dexamethasone or other steroid administration (Yes/No), start date and end date (MM/DD/YYYY, as available) - Indicator of siltuximab, anakinra, and/or methylprednisolone administration (Yes/No)	During Elra-containing LOT

Peripheral Neuropathy	Outcome	- Treatment: - Indication of administration neuropathic pain medication (Yes/No)	During Elra-containing LOT
Bacterial Infection	Outcome	- Treatment: - Indication of administration of antibiotics (Yes/No)	During Elra-containing LOT
Viral Infection (non-COVID)	Outcome	- Treatment: - Indication of administration of antiviral medications (Yes/No)	During Elra-containing LOT
Hypogammaglobulinemia	Outcome	- Evidence of hypogammaglobulinemia (Yes/No) - Treatment: - Indication of administration of Ig replacement therapy (Yes/No) Note: Severity information will not be available for this rWAE.	During Elra-containing LOT
Baseline Variables and Other Covariates		Operational Definition	Assessment Period
Year of initial MM diagnosis	Baseline characteristic	Categorical: 2013-2015 2016-2018 2019-2021 2022 2023 2024 2025	At initial diagnosis of MM

Age at index date	Baseline characteristic	Age at index date (continuous) - Definition: Age at the index date is calculated as: Age = Year of index date – BirthYear (from Redacted Demographics table). - Source and Transformation: BirthYear reflects the year of birth recorded in the EHR. Note: To meet de-identification requirements, Redacted transforms the BirthYear of patients older than 85 years at the data cutoff year. Approximately 9% of patients may have a transformed BirthYear, with a median difference of four years (IQR: 2–6 years). It is not possible to identify which records were transformed [13]. Implication for calculation: For patients with $\text{BirthYear} \leq (\text{data cutoff year} - 85)$, the calculated age should be considered a minimum estimate (eg, “$\geq$ calculated age”).	At index date
Age at index date	Baseline characteristic	Age at index (categorical) < 81 ≥ 81 Note: To meet de-identification requirements, Redacted transforms the BirthYear of patients older than 85 years at the data cutoff year. Approximately 9% of patients may have a transformed BirthYear, with a median difference of four years (IQR: 2–6 years). It is not possible to identify which records were transformed [13]. Implication for calculation: For patients with $\text{BirthYear} \leq (\text{data cutoff year} - 85)$, the calculated age should be considered a minimum estimate (e.g., “$\geq$ calculated age”).	At index date
Birth sex	Baseline characteristic	Patient sex: - Male - Female - Unknown Note: Values in the sex variable likely reflect a patient’s sex at birth, which reflects limitations in how EHR software systems have collected sex and gender identity information.	As of index date

Race	Baseline characteristic	Patient race: • White • Black or African American • Asian • Other Race • Unknown Note: "Other Race" includes patients who identified as American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander, or mixed races	As of index date
Patient region	Baseline characteristic	• Midwest • South • West • Northeast • Unknown States are mapped to regions based on USA Census Bureau Note: Patients from academic practices have unknown state values.	As of index date
Ethnicity	Baseline characteristic	Patient ethnicity: • Not Hispanic or Latino • Hispanic or Latino • Unknown	As of index date
Socioeconomic status (SES)	Baseline characteristic	Based on the SES index, which is an area-level measure that provides insight into the socioeconomic conditions of the neighborhoods where patients reside. Provides the relevant SES Index quintile for a patient's block group based on 2015-2019 Census data: • 1 - Lowest SES • 2 • 3 • 4 • 5 - Highest SES	As of index date
Insurance type at index	Baseline characteristic	Insurance type: • Commercial/Private • Medicare • Medicaid • Other government programs (eg, VA, Military, Tricare) • Self-pay/Uninsured • Unknown/Missing	As of index date

Practice type at index	Baseline characteristic	Practice type: - Academic - Community - Both	As of index date
Body mass index (BMI) at Index	Baseline characteristic	Continuous (kg/m ²), calculated based on structured data or patients' height and weight from the Vitals table. Determined using WHO BMI Categories: - Underweight: <18.5 (May reflect frailty or cachexia; often rare in MM) - Normal Weight: 18.5-24.9 - Overweight: 25.0-29.9 (Mildly elevated risk for some AEs) - Obese (Class I-III): ≥30.0	The baseline window for BMI will start 30 days prior to index date and end 7 days after index date. The closest BMI value to index date within the time window will be used. If the absolute time difference is the same, the BMI value that precedes the index date will be used. For patients with multiple BMI values on the same day, the highest eligible BMI value will be selected.
Eastern Cooperative Oncology Group (ECOG) at index	Baseline characteristic	ECOG performance status (PS) on or prior to index date: 0 1 ≥ 2 - Unknown	The baseline window for ECOG will start 30 days prior to index date and end 7 days after index date. The closest ECOG value to index date within the time window will be used. If the absolute time difference is the same, the ECOG value that precedes the index date will be used. For patients with multiple ECOG values on the same day, the highest eligible ECOG value will be selected.
International Staging System (ISS) stage at initial diagnosis	Baseline characteristic	- Stage I - Stage II - Stage III - Unknown/not documented	Baseline period
Monoclonal protein (M-spike) testing	Baseline characteristic	Test closest to index date (latest test on or prior to index date): - Date electrophoresis test - Specimen collected for each electrophoresis test (serum, urine, unknown/not documented) - Documented and standardized units - M spike value - Immunofixation results - TestID	Baseline period For patients with multiple M-spike tests within the baseline period, the test value on or closest to the index date will be selected. If there are multiple tests on the same day, the highest value will be used.

FISH cytogenetics testing	Baseline characteristic	Test closest to index date (latest test on or prior to index date): • Date of specimen collection • Indication of testing and whether abnormalities were identified (e.g., present, absent) for the following markers: t(14;16), t(11;14), t(4;14), t(6;14), t(14;20), deletion 17p, deletion 13q, deletion 1p, amplification 1q21, trisomy, other chromosome 1 abnormalities	Baseline period For patients with multiple FISH cytogenetics tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Karyotyping	Baseline characteristic	Test closest to index date (latest test on or prior to index date): • Date of specimen collection • Indication of testing and results for: ○ Number of chromosomes ○ Detection of abnormalities: trisomy, deletion 13 ○ Ploidy: hyperdiploid, hypodiploid, unknown, not documented	Baseline period For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Cytogenetic risk category	Baseline characteristic	Recently, in September of 2025, the International Myeloma Society (IMS) and the International Myeloma Working Group (IMWG) have released new recommendations for defining high-risk MM based on genomic tools. This new consensus definition, known as IMS-IMWG Consensus Genomic Staging (CGS), aims to more accurately identify patients with a poor prognosis [14]. Recognizing that RWD sources may not fully capture the granular detail required by the 'new' high-risk cytogenetic definition, we will employ a dual classification approach, integrating both the established ('old') and revised ('new') criteria for this study. <i>New Definition</i> The IMS-IMWG CGS of high-risk MM requires sequencing-based analyses and relies on the presence of at least one of the following abnormalities:	Baseline period Cytogenetic classification is based upon cytogenetic tests prior to and up to 60 days after the diagnosis date. For patients with multiple tests within the assessment period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.

		- del(17p) with a clonal fraction greater than 20%, a TP53 mutation, or both.* - An IgH translocation, including t(4;14), t(14;16), or t(14;20), along with gain or amplification of the long arm of chromosome 1 (1q+), del(1p32), or both. - Monoallelic del(1p32) along with 1q+ or biallelic del(1p32).** - High levels of β2-microglobulin (≥ 5.5 mg/L) with normal creatinine (< 1.2 mg/dL). <i>The guidelines also emphasize the importance of genomic sequencing for all MM patients and recommend that FISH testing be performed on plasma cell-enriched samples with a minimum purity of 70%. Risk assessments should be conducted at both diagnosis and relapse, with testing currently limited to bone marrow samples.</i> <i>*This will not be available in the current dataset.</i> <i>**The cytogenetic abstraction approach of the current dataset does not get to the level of granularity of monoallelic or biallelic deletion.</i> Old Definition Cytogenetic classification adapted from mSMART treatment guidelines and National Comprehensive Cancer Network (NCCN) Guidelines (Dispenzieri et al., 2007; Kumar et al., 2009; Mikhael et al., 2013; mSMART 2023; NCCN 2023) - High risk: FISH del 17p, t(4;14), t(14;16), t(14;20), 1q21 gain/1q21 amplification - Standard risk: t(11;14), t(6;14), trisomy - Unknown: patients without documented cytogenetic tests Note: Cytogenetic classification is based upon cytogenetic tests prior to and up to 60 days after the diagnosis date.	
Myeloma protein Ig class	Baseline characteristic	Patient's protein Ig class	Baseline period

		• IgA • IgD • IgE • IgG • IgM • Not Documented Note: These categories are not mutually exclusive and patients may present with multiple Ig classes for their myeloma proteins. Thus, each category may be displayed separately in results.	For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Involved light chain type	Baseline characteristic	Patient's involved light chain type • Kappa • Lambda • Not Documented Note: These categories are not mutually exclusive and patients may present with multiple involved light chain types. Thus, each category may be displayed separately in results.	Baseline period For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Oligosecretory status (<i>exploratory variable</i>)	Baseline characteristic	Based on existed reports [15, 16], Oligo-Secretory Disease Status will be defined as Serum M protein < 1 g/dL AND urine M protein < 200 mg/day. • Handling: ○ Latest Urine Protein Electrophoresis (UPEP) and Serum Protein Electrophoresis (SPEP) from baseline will be used ○ Make sure tests have valid units (mg for UPEP, g/dL for SPEP). ○ For FLC: latest serum test (kappa or lambda), mg/L units, elevated if outside normal range; but since the ratio itself cannot ensure that one type of FLC is elevated or low, we wouldn't be able to rely on this alone to identify FLC elevated Looser Definitions (<i>if full capture for above is not possible</i>): • Allow either UPEP or SPEP instead of requiring both.	Baseline period For patients with multiple tests within the baseline period, the test value closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Light chain MM (LCMM) status (<i>exploratory variable</i>)	Baseline characteristic	• Based on existing reports [15, 16], LCMM Status will be defined as Absence of M spike AND elevated FLC (kappa or gamma).	Baseline period

		○ Free kappa light chain (normal 3.3 – 19.4 mg/l) ○ Free lambda light chain (normal 5.71 – 26.3 mg/l) ○ Free kappa/lambda ratio (normal 0.26-1.65 mg/l) Handling: • Use latest UPEP, SPEP, and FLC from baseline. • For Mspike: no unit restriction since we are interested in tests that did not identify presence of Mspike; if multiple assessments same day, keep one with M spike detected; use IFEM spike if Mspike missing. • For FLC: latest serum test (kappa or lambda), mg/L units, elevated if outside normal range ; but since the ratio itself cannot ensure that one type of FLC is elevated or low, we wouldn't be able to rely on this alone to identify FLC elevated Looser Definitions <i>(if full capture for above is not possible)</i>: • Allow either UPEP or SPEP instead of requiring both. • For FLC: Consider dropping ratio criterion and rely on kappa/lambda only.	For patients with multiple tests within the baseline period, the test value closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.
Renal impairment	Baseline characteristic	Categorical, using National Kidney Foundation (NFK) criteria and structured lab values. The NFK defines renal impairment as: • G1: glomerular filtration rate (GFR) 90 mL/min/1.73 m² and above with evidence of kidney disease, such as hematuria or proteinuria • G2: GFR 60 to 89 mL/min/1.73 m² • G3a: GFR 45 to 59 mL/min/1.73 m² • G3b: GFR 30 to 44 mL/min/1.73 m² • G4: GFR 15 to 29 mL/min/1.73 m² • G5: GFR less than 15 mL/min/1.73 m² or treatment by dialysis For the current study, categories will be collapsed, as follows: Moderate RI or no RI	Baseline period For patients with multiple tests within the baseline period, the test value on or closest to index date will be selected. If there are multiple tests on the same day, the highest value will be used.

		- No RI: CrCl ≥ 40 mL/min - Moderate RI: CrCl 30–39 mL/min Severe RI - Severe RI: CrCl < 30 mL/min - Dialysis	
Presence of extramedullary disease at diagnosis	Baseline characteristic	- Yes - No	As of diagnosis date For patients with multiple tests within the baseline period, the test value on or closest to diagnosis date will be selected.
Charlson comorbidity index (CCI) Score	Baseline characteristic	Assessed at any time prior to index date: CCI score, a derived measure created from the list of CCI comorbidities identified via ICD-9 and/or ICD-10 codes (Please see Annex 3 for more details). 0: no comorbidity 1-2: moderate ≥ 3: high burden	As of index date
Simplified frailty score	Baseline characteristic	Frailty will be evaluated using the simplified frailty score described by Facon et al. [17], which incorporates age, CCI, and ECOG PS. Age, CCI, and ECOG PS are each categorized according to predefined thresholds, and points are assigned to each category. The total frailty score is calculated by summing the points from all three components.* Patients are then classified as frail or non-frail based on the total score, with higher scores indicating greater frailty. This classification will be used to stratify patients for efficacy and safety analyses. - Non-frail: 0 - 1 - Frail: ≥ 2 *Relevant details regarding how points will be assigned to each factor: - Age: ≤ 75 yrs = 0 points 76-80 yrs = 1 point > 80 yrs = 2 points - CCI: ≤ 1 = 0 points > 1 = 1 point - ECOG PS: 0 = 0 points	As of index date

		○ 1 = 1 point ○ ≥ 2 = 2 points	
Prior receipt of Chimeric Antigen Receptor T (CAR T)-cell therapy	Baseline characteristic	Indicates whether a patient received treatment with CAR T-cell therapy at any time prior to the index LOT: • Yes • No	Baseline period
Penta-drug exposure	Baseline characteristic	Indicates whether a patient had penta-drug exposure prior to the index LOT, defined as follows: • ≥ 2 distinct treatment(s) for PIs (bortezomib, carfilzomib, or ixazomib) • ≥ 2 distinct treatment(s) for IMiDs (lenalidomide, thalidomide, or pomalidomide) • ≥ 1 treatment(s) for CD38 mAbs (daratumumab, isatuximab)	Baseline period
Prior receipt of autologous Stem cell transplant (SCT)	Baseline characteristic	Indicates whether a patient received autologous SCT at any time prior to the index LOT: • Yes • No	Baseline period
Prior receipt of allogeneic SCT	Baseline characteristic	Indicates whether a patient received allogeneic SCT at any time prior to the index LOT: • Yes • No	Baseline period
Treatment Patterns		Operational Definition	Assessment Period
Number of lines of systemic therapy prior to index LOT	Baseline characteristic	Median with range Categorical, number of LOTs received prior to the index date: • 3 • 4 • 5+	Baseline period
Prior treatments	Baseline characteristic	For each prior LOT: • Number of Line • Drug class(es) received • Treatment sequencing via Sankey diagrams • Autologous SCT received prior to LOT (y/n) • Allogeneic SCT received prior to LOT (y/n)	Baseline period
Index regimen	Exposure	Full regimen received in index LOT (first elra-containing LOT)	Index LOT

First subsequent LOT after receiving Elra	Exposure	Subsequent 1st LOT following Elra treatment: • Drug class(es) received • Top 20 specific treatment regimens received • Autologous SCT received prior to LOT (y/n) • Allogeneic SCT received prior to LOT (y/n) • The number of patients with no subsequent LOT after the elra-containing LOT will also be reported	From the initiation of a new LOT after the end of the Elra-containing LOT
Time from initial MM diagnosis date to index Elra treatment	Baseline characteristic / Exposure	Time (in months) from the initial diagnosis of MM to the start date of the index LOT (first Elra-containing line).	Baseline period to index date
Duration of treatment with Elra	Effect modifier	Time (in months) from the first administration of Elra to last administration of Elra	As of index date
Setting of care for Elra administration	Sub-group identifier	Reported for step-up dose 1, step-up dose 2, and the first treatment dose of Elra; categorical: • Inpatient • Outpatient • Not documented	Index LOT
Timing of dosing periods	Effect modifier	Timing of the various dosing periods will be reported (for patients with the available follow-up time) • Index date (day 1) to day 8: defined as the first 8 days post-index date, inclusive. Also defined as day 1 to day 8. (STEP UP DOSE PERIOD) • Day 9 to day 168: defined as the period from day 9 to day 168 post-index date. (aka MAINTENANCE PERIOD 1 – the period in which Elra would be expected to be administered once weekly) • Day 169+: defined as the period from day 169 post-index date to end of follow-up period. (aka MAINTENANCE PERIOD 2 – the period in which Elra would be expected to be administered every 2 weeks Q2W depending on individual response) • Overall follow-up (day 1 to end of follow-up period): defined as the period from index date to end of follow-up period	Follow-up period

Dosing	Effect modifier	Reported for each administration of Elra, including step-up doses; distribution of dosing: • 12 mg • 32 mg • 76 mg • Not recorded	During Elra containing LOT
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8.4. Data Sources

As recommended in the draft FDA Guidance for Industry RWD: Assessing EHRs and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products (September 2021), a description of the [REDACTED], data source management, and processing are provided.

The [REDACTED] is a longitudinal database derived from EHRs and other RWD sources from cancer care providers across the US. [REDACTED] is classified as structured or unstructured. Structured data refers to data points that are organized in a predefined manner, such as drop-down fields that reside in an EHR (e.g., a patient's sex or date of birth). [REDACTED] harmonizes structured data to a standard terminology. Structured data is not provided directly to sponsors in the delivery of real-world datasets. Unstructured data refers to information that is not organized in a pre-existing field, such as free text from physician notes, or other non-standardized information in computer documents (such as PDF-based radiology reports) in an EHR. Unstructured data is not provided directly to sponsors in the delivery of real-world datasets.

The patient population within the [REDACTED] evolves over time, based on the patients cared for in the [REDACTED] network practices. Only patients from practices that have given [REDACTED] appropriate data rights are included in the [REDACTED]. For patients treated in the [REDACTED] network, the entire patient chart in the EHR is available to [REDACTED], enabling a longitudinal data view of patients' health care with resolution at the disease and treatment level. Characteristics of patients in the [REDACTED] have been compared to other data sources, such as Surveillance, Epidemiology, and End Results Program (SEER) and National Program for Cancer Registries (NPCR), and found to be broadly representative [18].

8.5. Study Size

After applying all inclusion/exclusion criteria, there will be approximately 120 patients available for the overall cohort. This study will use descriptive statistics to estimate the outcomes; thus, no sample size calculations were conducted.

8.6. Data Management

[REDACTED] employs an Extract, Transform, and Load (ETL) process, a series of operations that move raw data from its source systems into [REDACTED]'s research databases to prepare structured data for use in real-world datasets.

The ETL process primarily leverages Structured Query Language (SQL), a [REDACTED] Health proprietary orchestration tool, and Python to process data in a consistent and reproducible manner. Through ETL, structured data is harmonized using domain-specific mapping policies to conform to a common data model, enabling disparate data sources to be integrated into a single, standardized dataset. Structured data are extracted from multiple EHR systems and other external supplementary sources. The mechanisms and cadence of extraction vary by source system. Defined business logic governs how data is extracted for each EHR type. To ensure reliability, the extraction process is monitored through automated alerting mechanisms that check whether data are extracted at the expected cadence and

accurately reflect their source. Any anomalies detected through these alerts are investigated and remediated as needed.

Once extracted, structured EHR data fields are transformed and standardized to ensure suitability for downstream research deliverables. This includes mapping data elements such as diagnoses, laboratory values, and medication administrations to a common vocabulary, normalizing them across different EHR systems. **Redacted**'s medical informatics mapping process establishes this common vocabulary. For example, multiple "albumin" terms captured across EHRs are harmonized into a single standardized albumin variable. Terms referring to different concepts (eg, albumin-related but not equivalent measures) are excluded from that mapping. **Redacted** uses a technology-enabled mapping system that automates terminology management, supplemented by manual review and quality control (QC) from **Redacted**'s technical and medical informatics teams. Items that cannot be automatically mapped undergo manual adjudication to ensure accuracy. In the load phase, the transformed and harmonized structured data are published as a research-ready dataset at a cadence aligned with project needs.

Before publication, the dataset undergoes both automated and manual quality checks. For example, new builds are compared to prior versions to identify unexpected changes in data volume, composition, or quality (eg, unusually high proportions of nulls in specific fields). More granular analyses may also be performed, for instance, evaluating additions or drops of specific LOINC codes for particular sites in the laboratory table, to ensure data stability and integrity across releases.

8.7. Data Analysis

8.7.1. Overview of Analysis

All analyses will be primarily descriptive in nature. Descriptive statistics will be used to summarize patient characteristics, treatment patterns, effectiveness outcomes (rwORR, OS, PFS), and adverse events (AE) endpoints overall and within subgroups. Analyses will be completed using R version 4.1.3.

Derived and Transformed Data

Patients' treatment will be derived using **Redacted** LOT business rules. Specifically, an oncologist-defined, rule-based approach is applied to sequences and combinations of abstracted oral therapy spans, medication administrations, and non-cancelled medication orders. These business rules are developed specific to MM. Generally, 5L+ treatment is defined based on the first systemic Elra administration after receiving at least 4 prior lines of treatments. Evidence of prior treatment is included to allow for minor misclassification of the number of LOTs.

Patients' baseline comorbidities will be summarized by CCI score, which will be a derived measure created from the list of CCI comorbidities identified via ICD-9 and/or ICD-10 codes (see [Annex 3](#)).

Bias Control Procedures:

- Selection bias: Transparent patient attrition counts will be reported; patients who do not meet the inclusion criteria will be excluded.
- Information bias: Only lab values with valid units will be used, an explicit "Not documented" category will be reported where applicable.
- Confounding: This analysis is primarily descriptive and no comparison models will be performed.
- Censoring bias: Consistent Kaplan-Meier censoring rules as defined in Section 8.7.2 will be applied where applicable.

8.7.2. Primary Analyses

Demographics and clinical characteristics

Baseline demographic and clinical characteristics will be described for the overall study cohort. Continuous variables will be described in terms of means, medians, IQR, SD, and range. Categorical variables will be reported as patient numbers and percentages of the population. Variable categories and definitions are described above in [Table 1](#) of this protocol.

Additional Details on Demographic and Clinical Characteristics:

- BMI will be assessed as a continuous variable (kg/m^2), calculated from structured data or patients' height and weight from the Vitals table. BMI will be categorized according to WHO criteria: Underweight (<18.5 ; may reflect frailty or cachexia and is often rare in MM), Normal Weight ($18.5\text{--}24.9$), Overweight ($25.0\text{--}29.9$; mildly elevated risk for some AEs), and Obese (Class I–III; ≥ 30.0).
- ECOG performance status (PS) will be assessed on or prior to the index date and included in all baseline summaries.
- Charlson Comorbidity Index (CCI) will be assessed at any time prior to the index date. CCI will be derived from ICD-9 and/or ICD-10 codes (see Appendix B for details) and categorized as follows: 0 (no comorbidity), 1–2 (moderate), and ≥ 3 (high burden).
- Frailty will be evaluated using the simplified frailty score described by Facon et al., which incorporates age, CCI, and ECOG PS. Each component will be categorized according to predefined thresholds and assigned points. The total frailty score will be calculated by summing the points from all three components. Patients will be classified as non-frail (score 0–1) or frail (score ≥ 2), and this classification will be used to stratify patients for efficacy and safety analyses.
- Renal impairment will be assessed according to IMWG criteria: serum creatinine >2.0 mg/dL (177 $\mu\text{mol}/\text{L}$) or creatinine clearance <40 ml/min (by Cockcroft-Gault or LOINC).
- Cytogenetic classification will be based on cytogenetic tests performed prior to and up to 60 days after the diagnosis date. For patients with multiple tests within the assessment period, the test value on or closest to the index date will be selected; if multiple tests occur on the same day, the highest value will be used. High-risk and standard-risk categories will be assigned according to both the IMS-IMWG Consensus Genomic Staging (September 2025) and legacy mSMART/NCCN guidelines. High-risk features will include FISH del 17p, t(4;14), t(14;16), t(14;20), and 1q21 gain/amplification. Standard risk will include t(11;14), t(6;14), and trisomy. Patients without documented cytogenetic tests will be classified as “unknown.”
- Oligo-Secretory Disease Status will be explored and defined as serum M protein <1 g/dL AND urine M protein <200 mg/day. The latest UPEP and SPEP from baseline will be used, ensuring valid units (mg for UPEP, g/dL for SPEP). For free light chain (FLC), the latest serum test (kappa or lambda) in mg/L units will be included and considered elevated if outside the normal range. If full capture is not possible, either UPEP or SPEP will be allowed instead of requiring both.
- LCMM Status will be explored and defined as absence of M spike AND elevated FLC. The latest UPEP, SPEP, and FLC from baseline will be used. For Mspike, no unit restriction will be applied; if multiple assessments occur on the same day, one with M spike detected will be retained, and IFEM spike will be used if Mspike is missing. For FLC, the latest serum test (kappa or lambda) in mg/L units will be included and considered elevated if outside the

normal range. If full capture is not possible, either UPEP or SPEP will be allowed instead of requiring both, and the ratio criterion may be dropped in favor of kappa/lambda only

Treatment patterns

Treatment patterns will be displayed in Sankey diagrams with corresponding tables presenting frequency and proportion of treatment type (both drug classes and top 20 individual regimens) by line. Sankey diagrams illustrate cohort-level switch to next treatment or no subsequent treatment due to death or censoring at last confirmed activity captured in the EHR. The number and proportion of patients who proceed to subsequent LOT will be described by line names. Patients who receive autologous and allogeneic SCT prior to each LOT will be described among patients receiving each LOT of interest.

For the index line (first Elra-containing line), the line number will be noted, as well as the full regimen received. Time from the end of the prior LOT to the start of the index LOT will be reported in days. Duration of treatment with Elra will be reported in months. For step-up dose 1, step-up dose 2, and the first treatment dose of Elra, setting of care and practice setting will be reported.

Additional Details on Index Treatment:

- The line number in which the index treatment (first Elra-containing regimen) occurred will be reported.
- The number and percentage of patients with evidence of elranatamab use prior to 5L+ will be reported. If substantial, a sensitivity analysis excluding these patients from rwORR and safety assessments will be performed.
- Timing of dosing periods will be reported for patients with available follow-up:
 - Step-up dose period: Index date (day 1) to day 8 (first 8 days post-index, inclusive)
 - Maintenance Period 1: Day 9 to day 168 (once weekly)
 - Maintenance Period 2: Day 169+ (every 2 weeks Q2W depending on response)
 - Overall follow-up: day 1 to end of follow-up period
- Doses will be reported for each administration of Elra, including step-up doses; distribution of dosing: 12mg, 32mg, 76mg, not recorded.
- Setting of care for Elra administration will be reported for step-up dose 1, step-up dose 2, and first treatment dose.
- Index LOT treatment duration is defined as length of time from index date to earliest of date of death, last confirmed activity date (vital information, medication administration, lab result, or last abstracted therapy date), initiation of new LOT, or data cutoff.
- Practice type for patients receiving Elra treatment will be captured.

Real world endpoints and outcomes: rwORR, rwPFS, rwOS

rwORR:

rwORR will be reported as the number and proportion of patients who have at least one rwPR or rwVGPR or better during the index LOT out of the total number of patients in the cohort, along with 95% confidential interval (CI) estimates. Each rwR category will also be reported among patients with available response information.

Additional Details on rwORR Capture:

- rwORR will be defined as the proportion of patients who had at least one PR, VGPR, or better assessment, among patients with a baseline lab value and a subsequent lab value.
- PR and VGPR will be derived from enhanced M spike and free light chain lab values based on IMWG criteria.

rwPFS:

rwPFS will be estimated among all patients in the study cohort using the Kaplan-Meier (KM) product limit estimator. Unadjusted Kaplan-Meier curves will be generated along with a tabular summary of the number of patients at-risk. The primary outcome reported will be median rwPFS and the corresponding 95% CIs. Landmark KM estimates of rwPFS and rwOS at 6, 12, and 18 months along with 95% CIs will be reported as secondary outcomes.

Additional Details on rwPFS:

Unlike solid tumors, the clinical standard for assessing progression in multiple myeloma relies primarily on changes in M spike levels in the blood or urine as measured by protein electrophoresis. When leveraging structured lab data alone, this lab value is missing or incomplete in a high percentage of patients. As a result, completeness of M spike has downstream implications on analyses that are evaluating outcomes, such as progression. Given the incompleteness of M spike in structured data, abstraction is used to increase capture of this lab data.

Redacteds approach described below is informed by International Myeloma Working Group (IMWG) criteria and incorporates both abstracted M spike lab values as well as structured free light chain (FLC) lab values for patients with multiple myeloma that is not detectable via M spike. Progression events are derived independently of line of therapy

To establish a baseline (nadir) for progression monitoring, specimens are selected in the following order of priority:

- 1st Choice (SPEP): Serum M-spike 1.0 g/dL.
- 2nd Choice (UPEP): 24-hour urine M-spike 200 mg.
- 3rd Choice (sFLC): The difference between kappa and lambda light chains (used only if M-spike is non-measurable).

Progression is identified by comparing subsequent labs to the lowest recorded value (nadir). To trigger a progression event, both conditions (Relative and Absolute increase) must typically be met:

Table 2. Lab Type for M-spike

Lab Type	Relative Increase (Condition A)	Absolute Increase (Condition B)
SPEP	≥25% increase over nadir	≥0.5 g/dL (if nadir <5) or ≥1.0 g/dL (if nadir ≥5)
UPEP	≥25% increase over nadir	≥200 mg/24 hours absolute increase
sFLC	≥25% increase in FLC difference	>10 mg/dL absolute increase in difference

Progression must be assessed using the same specimen type as the baseline (e.g., if baseline was SPEP, only SPEP is used for rwPFS). The first progression-eligible lab must occur > 14 days after the baseline to avoid capturing early fluctuations.

rwOS:

rwOS will be estimated among all patients in the study cohort using the KM product limit estimator. Unadjusted KM curves will be generated along with a tabular summary of the number of patients at-risk. The primary outcome reported will be median rwOS and the corresponding 95% CIs. Landmark KM estimates of rwOS at 6, 12, and 18 months along with 95% CIs will be reported as secondary outcomes.

Additional Details on rwOS

rwOS is the time from the index date to the date of death, regardless of cause. For patients without a recorded date of death, rwOS is censored at the last confirmed EHR activity date. rwOS event dates are determined using Redacted's composite mortality variable, which combines structured EHR-derived mortality data (e.g., documented date of death), abstracted information from available EHR documentation, and data from external sources including the Social Security Death Index (SSDI) and obituary data (processed from funeral homes and other sources). The last confirmed activity date (censor date) is defined as the latest of: (1) last recorded structured activity (vital information, medication administration, laboratory test/result), or (2) last abstracted oral therapy date. For purposes of de-identification, date of death is provided at month-level granularity and is generalized to the middle of the month. Details regarding Redacted mortality variable are presented in ANNEX 3. Mortality Additional Information.

Adverse Events:

Incidence of real-world AEs will be reported as the number and proportion of patients with first onset or worsening of the selected rwAE type that occurred during the follow-up period. The window for rwAE capture will be 30 days prior to the start of the line (for the AE to be considered present at baseline) through the end of the LOT. Numbers and proportions of patients with a drug-attributable (ie, "definite attribution" and "likely attribution," respectively) rwAE will also be reported.

The proportion of patients with documented presence of each rwAE type and type of outcome related to the rwAE (including therapy discontinuation, dose or schedule change, therapy hold, treatment for the rwAE, and hospitalization) will be presented. Therapy attribution of rwAEs will be reported as numbers and proportions of patients by each rwAE type and therapy attribution category, including definite attribution, likely attribution, not attributed, and no documentation. Resolution of rwAEs will be reported as the proportion of patients with each documented resolution status type (resolved, resolving, resolved with sequelae, ongoing, fatal, not documented), for each rwAE. Time to resolution will be reported in days for those rwAEs that are noted to be resolved or resolved with sequelae.

Additional Details on rwAE Capture:

- Baseline rwAE prevalence: The number and proportion of patients who have evidence of the respective rwAE during the baseline period (defined as 30 days prior to index LOT up to one day before index LOT) will be reported.
- Incident rwAEs: The number and proportion of patients without any pre-existing rwAEs (no occurrence of the AE within 30 days prior to the index date) who experience one or more rwAE during the AE examination period will be calculated and divided by the total number of patients in the cohort.
- Worsening of pre-existing rwAEs: The number and proportion of patients with one or more pre-existing rwAEs who experience a worsening of the rwAE (or worsening of one or more of the pre-existing rwAEs) during the AE examination period will be calculated and divided by the total number of patients in the cohort. Worsening is defined as the AE being present at baseline and documented to be worse/increased compared to baseline status, or the AE is present at baseline, resolves, and then recurs during the AE examination period.

- Clinician-documented outcomes: Outcomes related to the selected rwAEs that occurred during the index LOT, as determined by abstraction, will include: dose or schedule change, therapy hold, therapy discontinuation, treatment for the AE, hospitalization, and no outcome related to the AE. These categories are not mutually exclusive and more than one can be selected and reported.
- Therapy attribution: The level of attribution for the selected rwAE of interest, as determined by the treating clinician, will be reported for each rwAE type: definite attribution, likely attribution, not attributed, and no documentation.
- Severity: The severity of the selected rwAE of interest, as determined by the treating clinician, will be reported for each rwAE type.
- Resolution status and timing: Clinician-documented resolution status of the selected rwAE of interest will be reported for each rwAE type: resolved, resolving, resolved with sequelae, ongoing, fatal, not documented. Time to resolution (in days) will be calculated from rwAE start to date of resolution for rwAEs marked as "resolved" or "resolved with sequelae".

Time from Elra start date to onset or worsening of rwAEs will be estimated using Kaplan-Meier methods. Time-at-risk will be indexed to Elra initiation, and the onset date of the specific rwAE. Patients without evidence of the rwAE will be censored at the end of the LOT. Median time to onset of rwAE and the corresponding 95% CI will be reported. In the event that the rwAE is resolved, median time to resolution of the rwAE and the corresponding 95% CI will also be reported.

8.7.3. Secondary Analyses

The same outcomes analysis as the above will be conducted in the following subgroups: Presence of extramedullary disease, high cytogenetic risk, performance status, renal impairment (*if sample size allows*), age (81 years of age and older), and setting of care for Elra step-up dose administration (inpatient vs. outpatient). They will also be conducted in the following groupings, conditional on outcomes: severity of AEs, safety grade 2 and above (*only available for ICANS and CRS*), and CRS and ICANS by setting of care for Elra step-up dose administration. rwAE incidence rates and related AE outcomes across subgroupings will be summarized descriptively.

8.7.4. Sensitivity Analyses

To maximize sample size for the current study, all patients meeting criteria up to the data cutoff date (June 30, 2025) will be included, without applying a criterion to allow for minimum potential follow-up time. To address this we will conduct two sensitivity analysis: one, where we rerun the rwORR and rwAE analyses restricting the cohort to patients indexed at least 3 months prior to data cutoff, and then a second rwORR and rwAE analyses including only those indexed at least 6 months prior to data cutoff to see the impact of follow-up time on the results.

Elra was approved on 14 August 2023 as a 5L+ regimen for the treatment of RRMM. To examine potential off-label use of Elra, the number and percentage of patients who have evidence of Elra use prior to 5L+ will be reported. If there is a substantial number, we can potentially run a sensitivity analysis excluding these patients from the rwORR and safety assessments.

If there is a substantial number of patients who received Elra prior to 5L+, as described above, we will potentially characterize this subgroup with some key baseline characteristics, and some basic treatment patterns, including the LOT in which Elra was received.

Any safety information deemed to be reportable as defined in this protocol will be described.

8.8. Quality Control

Redacted is committed to conducting high quality research intended to comply with regulatory requirements, industry best practices, and internal quality commitments. These inputs drive the implementation and ongoing development, enhancement, and maintenance of the QMS. **Redacted**'s research QMS is derived from defined principles outlined in ICH guidance documents and life science industry best practices. **Redacted**'s QMS is the foundation for the oversight activities which occur throughout the research lifecycle that support integrity of **Redacted**'s software systems, the curation and cleaning of data originating from structured and unstructured data sources, and the conduct of analytic studies.

Redacted's quality assurance (QA) and QC activities aim to understand and improve the quality of our data, as well as provide oversight to the data collection process and conduct of analyses. Activities for this protocol fall into these categories:

- Operational procedures: These are documented processes which allow **Redacted** to employ consistency in completing tasks, anticipate potential roadblocks, as well as increase efficiency and facilitate planning.
- Quality procedures: These are processes intended to provide oversight of protocol-related activities to ensure that data are generated, documented (recorded), and reported in line with requirements (e.g., **Redacted**'s processes).
- System controls: These are processes built into technical systems and/or workflows to provide programmatic oversight and efficiency through (e.g., software).

Throughout the data lifecycle, **Redacted** employs both automated and manual monitoring to ensure data quality and integrity. Automated alerting mechanisms continuously check extraction cadence and data fidelity, flagging anomalies for prompt investigation and remediation. Prior to dataset publication, comprehensive quality checks—including comparisons to previous builds and granular analyses of data elements—are performed to detect unexpected changes or inconsistencies. These monitoring activities are supplemented by manual review and adjudication, ensuring that data meet rigorous standards for research.

8.9. Strengths and Limitations of the Research Methods

Strengths:

The addition of real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) as study outcomes substantially strengthens the clinical relevance and interpretability of this study. With sufficient follow-up accrued since study initiation (median follow-up >12 months), inclusion of time-to-event outcomes allows for a more comprehensive assessment of Elra effectiveness beyond response-based endpoints alone. rwPFS and rwOS provide clinically meaningful measures of disease control and survival in routine clinical practice, improving alignment with outcomes commonly used in clinical trials, for example.

The capture of prophylactic intravenous immunoglobulin (IVIG) use represents an important methodological enhancement to the safety evaluation, particularly for infection-related outcomes. Documenting prophylactic use of IVIG enables improved contextualization of observed infection incidence and severity in the Elra-treated cohort. This addition helps us to contextualize safety signals from effects attributable to proactive infection mitigation strategies.

Refinement of cohort definitions to explicitly distinguish immune effector cell-associated neurotoxicity syndrome (ICANS) from broader neurotoxicity (NT) further improves the clinical specificity and validity of safety outcomes. ICANS is a distinct, well-characterized clinical syndrome

with specific diagnostic and management considerations. Separating ICANS from non-ICANS neurotoxicity reduces potential misclassification, and allows for clearer interpretation of neurologic adverse event patterns associated with Elra in real-world practice.

Finally, the revised and expanded descriptions of progression and mortality ascertainment within **Redacted** data enhance transparency and reproducibility of rwPFS and rwOS analyses. Providing detailed operational definitions, data sources, and censoring rules improves interpretability of time-to-event outcomes and strengthens confidence in the robustness of survival analyses derived from real-world data.

Generalizability:

The data source for this study largely draws from community oncology centers in the US, though patients treated in academic practices are also included, which may lead to a skewed pattern of treatment (eg, less aggressive treatment tendencies). External validity may be limited as oncology practices included in this study are part of the database's oncology practice network, which may not represent all oncology practice sites within the US. Consequently, generalizability of the results to the overall US population as well as non-US populations may be limited. Also, although the present study is descriptive, the study cohort has small sample size which limits the ability to generalize to the target population as a result of increased random error.

Additionally, the patients with RRMM included in this study are heavily-pretreated, and the diversity of prior treatment exposures and sequencing strategies may influence the response outcomes with Elra. For example, variations in the timing and order of proteasome inhibitors, IMiDs, and anti-CD38 monoclonal antibodies, and other BCMA-targeted agents may affect subsequent disease biology and sensitivity to Elra. Such heterogeneity in treatment histories is difficult to fully control for in retrospective analysis, and therefore, caution should be exercised when attempting to evaluate rwORR and safety data across these Elra treatment cohorts.

Data Collection/Ascertainment

EHR-based data in the **Redacted** is collected primarily for the clinical management of oncology patients and not for research purposes. The proposed study is therefore subject to the availability and level of granularity provided in the source data and, by extension, in the **Redacted**. This means there may be data not included or not included at an optimal level of granularity for the purpose of analyses described in the proposed study.

Evidence of exposure to treatments may be limited in the **Redacted** if patients are treated outside of the **Redacted** clinical network. This may result in a misclassified line of treatments. However, capture of treatments from unstructured data (e.g., review of clinical notes) is used to mitigate the potential for this source of misclassification. Additionally, treatments for additional malignancies may be incorrectly included in a LOT as the rules are not able to attribute medication administration or orders to the disease of interest. This likely will not be an issue as regimens are selected based on known standards of care for MM.

Because the rwAEs assessed in the present study are identified *a priori*, additional rwAEs outside of the pre-specified list that occur will not be included. Further, information on the grade or severity of rwAEs will not be available to examine the incidence by grade or to contextualize the outcomes and management of the rwAEs.

Specific to the outcomes and management of rwAEs, ascertainment is dependent upon clinician documentation, which may be missing. Thus, it is possible that the proportion of patients who die or who are hospitalized due to a rwAE may be underestimated, as there could be cases in which this occurs, but it is not documented. For management of the rwAEs, structured data will be used to assess

treatments given to treat the rwAEs. The structured data cannot be confirmed as given for treatment of the rwAEs; thus, patients may be misclassified. This is mitigated by only assessing structured data in instances when patients have abstracted evidence confirming they received any treatment for the rwAEs and by only looking at structured data after the onset of the rwAEs.

Elra was approved on August 14, 2023, as a 5L+ regimen for the treatment of RRMM. As a result of the relatively recent approval, there are not enough patients in the **Redacted** to adequately characterize the incidence and outcomes of rwAEs in this population.

Measurement validity and granularity

Treatments for additional malignancies may be incorrectly included in the LOT rules specific to the MM. Tumor characteristics and/or diagnoses may be misclassified if the documentation in the patient chart was entered erroneously.

Missingness

The lack of availability of data on certain variables, missingness in data obtained from the EHR, and loss-to-follow-up could introduce bias due to unmeasured confounding. Relatedly, certain variables may not be available with full completeness, such as race, ethnicity, stage, and ECOG. Baseline comorbidities and CCI score carry methodological limitations due to the included conditions being identified via ICD-9 and -10 codes which are susceptible to under-reporting and missingness in this dataset. Other primary malignancies will be identified via ICD-9 and -10 codes and there may be a degree of missingness in their reporting.

Redacted's BirthYear Transformation may potentially impact the elderly patient population in this study. As outlined in [Table 1](#), **Redacted** adjusts BirthYear for elderly patients; therefore, some individuals may appear younger than their true age. This could result in an underestimation of age at index date for the oldest patients (≥ 85 years). All age-related analyses and interpretations will consider this limitation. If precise age information for elderly patients is critical, a custom data extract from **Redacted** may be requested under privacy safeguards.

LOT are derived from EHR data using **Redacted** Health oncologist-defined, rules-based algorithms based on structured medication administrations, structured non-cancelled orders, and abstracted oral/intravenous antineoplastic therapies. As a result, a patient's treatment assignment and/or sequencing may be misclassified if underlying treatment data is missing or if treatment is ordered but not received. And also, treatments received for additional primary malignancies (other than MM) may be incorrectly included in LOT.

Regarding Cytogenetic Risk Classification, the recently proposed IMS-IMWG CGS definition of high-risk MM incorporates genomic abnormalities beyond the traditional criteria. However, some of these variables are not available in the current dataset; in particular, del(17p) with a clonal fraction $>20\%$, TP53 mutation, or both, as well as monoallelic del(1p32) with 1q+ or biallelic del(1p32) are recognized as high-risk features, but are not captured. As a result, some patients who would be considered high risk under CGS may be misclassified as standard risk, potentially leading to an underestimation of the prevalence and impact of high-risk cytogenetics in our study. Nevertheless, by employing both established ("old") and revised ("new") definitions where feasible, we provide a pragmatic framework for cytogenetic risk stratification in the context of RWD.

IMWG frailty score is considered to be a strong prognostic indicator of clinical outcomes in MM. This frailty score is not a variable in the current dataset, as activities of daily living are not captured; however, the simplified IMWG frailty score consists of ECOG, CCI, and age. A retrospective observational study such as this one can only capture an abstracted rwAE if it is documented by the clinician in the EHR in the course of standard care. Additionally, only the first instance of an AE is abstracted when there is documentation of an AE multiple times while receiving the therapy of

interest. Clinicians may not document conditions that occur that do not result in changes in treatment relevant to that clinician's area of practice or do not result in a condition that is eligible for reimbursement of treatment. A condition also may not be reported to the clinician by a patient and therefore will not be reflected in this study. Attribution of the rwAE to the therapy is also only reported if it is documented by the clinician; as such, there will be a level of missingness associated with this variable.

In addition, patients may also be lost-to-follow-up if they seek treatment or care in practices outside of the [Redacted] network leading to potentially incomplete patient-level clinical information. As such, the end of clinical activities only reflects the most recent clinical activity as recorded by cancer care providers in the [Redacted]

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exists in a de-identified/anonymized structured format and contains no patient personal information.

9.2. Patient Consent

As this study involves de-identified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

IRB is not required for this study as it uses EHR available de-identified secondary data sources and is considered exempt from the requirements for "human subjects research" in the US.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices. [Redacted]'s dataset from which the data for this study was extracted is covered by the [Redacted] Health Real-World Evidence Parent Protocol approved initially by the New England IRB and then by Copernicus Group Independent Review Board. Additionally, a sub-study protocol was also submitted as a supplement in addition to the parent protocol and provided to the IRB for approval. IRB approval was in place for the duration of research activities and documentation for IRB submissions, approvals, and continuing review are retained by [Redacted] Health.

In addition, the study design and conduct are guided by the Guidelines for Good Epidemiologic Practice, including the 2005 FDA Good Pharmacoepidemiology Practices (GPP), Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, and the 2015 International Society of Pharmacoepidemiology GPP.[\[19-20\]](#)

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.*

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study Report

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Publication

The results of the present study will be used to develop an abstract to be submitted to the congress in 2026.

In collaboration with Pfizer, the manuscript will communicate the findings of the study conducted for the core task above. The **Redacted** project team will work closely with Pfizer to identify the most appropriate target journal for the manuscript.

Pfizer policy or guidance covering publications of study data will be observed to determine when and how the results will be communicated. Authorship for all publications will comply with ICMJE criteria. Each author will have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

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None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable/not required

ANNEX 3. ADDITIONAL INFORMATION

DESCRIPTION OF THE [REDACTED] DATA SOURCE AND OVERVIEW OF [REDACTED]

A.1 Introduction

The [REDACTED] is a longitudinal database derived from EHRs and other RWD sources from cancer care providers across the United States. [REDACTED] operates a real-world oncology data platform that aggregates and processes patient-level data such as demographics, diagnostic information, extent of disease, laboratory values, treatments, and patient outcomes. This detailed information facilitates insight into real-world cancer care, permitting hypothesis generation and retrospective research.

The primary source for [REDACTED] data is EHRs. De-identified data originated from approximately 280 US cancer clinics (~800 sites of care). The majority of patients in the database (approximately 75%) originate from community oncology settings; relative community/academic proportions may vary depending on study cohort.

Patients are routinely included in research datasets based on confirmation of defined criteria (eg, the type of tumor of interest and stage of disease). [REDACTED] employs data handling best practices to maximize the inclusion of relevant treatment history, as available in the patient's EHR. In addition to data available in the EHR, data from secondary sources (such as databases from commercial, government, claims, genomics, or other RWD sources of clinical information collected in the routine care of patients) may also be included.

[REDACTED] EHR data are classified as *structured* or *unstructured*.

- **Structured data** refers to data points that are organized in a predefined manner, such as drop-down fields that reside in an EHR (e.g., a patient's sex or date of birth). Redacted Health harmonizes structured data to a standard terminology. One specific example of harmonized data is diagnosis codes that are mapped to ICD-9 and ICD-10 codes. Structured data are not directly used in research deliverables for external sponsors.
- **Unstructured data** refers to information that is not organized in a pre-existing field, such as free text from physician notes or as other non-standardized information in computer documents (such as portable document format [PDF]-based radiology reports) in an EHR. Unstructured data are not directly used in research deliverables for external sponsors.

EHR data are processed using extraction, harmonization, abstraction, and/or derivation to create data variables of interest based on standardized processes. This results in the study-specific research dataset used in deliverables for external sponsors.

- **Extraction** results from retrieving data out of structured data or from the retrieval of unstructured data into structured data through automated techniques using artificial intelligence (eg, NLP and machine learning [ML]) and document searching techniques. Similar to abstracted data, extracted data supports Redacted Health's ability to incorporate key information from the EHR. Examples of extracted data are diagnosis codes, demographics, ECOG performance status, and laboratory results.
- **Harmonization** results when individual data elements are mapped to controlled vocabularies that support the clinical use case and translate data in a consistent way. This achieves semantic consistency and representation of oncology data to support interoperability, data quality, and accuracy. An example of harmonization is mapping disease stage using disease-specific staging systems such as American Joint Committee on Cancer, Ann Arbor Staging system, International Prognostic Scoring System, and others (based on the cancer type of interest).
- **Abstraction** results from the manual abstraction of unstructured data into structured data using specially trained human abstractors. Unstructured data are processed through Redacted Health's proprietary, technology-enabled abstraction software platform, which supports Redacted Health's ability to incorporate key information from the EHR (e.g., data points, clinician interpretation of digital images). Examples of abstracted data are disease stage, biomarker testing results, and oral antineoplastic therapies that are organized in discharge notes, physician notes, pathology reports, and other documents.
- **Derivation** results when multiple data components are combined with established deterministic rules. Examples of derived data include LOTs and patient date of death. One specific example of derived data is three different medications that are grouped together into a treatment sequence or LOT based on established deterministic rules.

A.2 Data management and processing

Following data extraction, harmonization, and abstraction, the processed data are used to create research cohorts, and the data are available for analysis. EHR data may also be linked to other external data sources (eg, genomics data and claims data).

Datasets comprising the combined extracted, harmonized, abstracted, and derived data are stored securely at Redacted Health or our data partners. Datasets are de-identified prior to use in deliverables shared with external research partners.

A.2.1 Structured data processing

Redacted Health uses an Extract-Transform-Load (ETL) process (i.e., a set of processes that are performed when moving raw data from its source into a database) for preparing structured data for real-world datasets. The ETL process primarily leverages SQL, a **Redacted** Health proprietary orchestration tool, and Python programming languages, which work with data in a consistently reproducible fashion. Structured data flows into the **Redacted** using the ETL process, during which data are harmonized using domain-specific mapping policies for specific mapping concepts to conform to a common data model. This allows disparate data sources to be output to a single, standardized dataset.

A.2.2 Unstructured data processing

Since there is an increased likelihood of patient information such as diagnosis, stage, histology, key outcomes, etc., being omitted if relying on structured EHR fields alone, **Redacted** Health has developed an approach to abstract unstructured data. Unstructured data are abstracted by specially trained human abstractors using Patient Manager®, **Redacted**’s proprietary software that supports the efficiency and accuracy of the process. Patient Manager® uses a layer of technology that facilitates document classification, visual organization, and abstraction workflow management. Indexed EHR documents are ingested from the EHR system, categorized (e.g., clinic note, pathology report), converted to a standard format (eg, PDF) with text extracted for digital recognition (e.g., optical character recognition) and stored in a central documents database. Data obtained through the abstraction of unstructured data are stored in the Patient Manager® Database.

Redacted data abstractors are qualified by training and experience, assessed through external experience (eg, direct experience with oncology and/or research) as well as **Redacted**-specific training and experience (eg, training on abstraction procedures, **Redacted** systems). Abstracted data are obtained from unstructured data using the Patient Manager® system in accordance with internal operating procedures (often referred to as abstraction P&Ps), documented best practice guidelines, and review/oversight controls. Documented processes, including oversight, tracking, and quality checks, are in place to optimize the quality of abstracted data.

A.2.3 Combining structured and unstructured data

After the above steps, the data is combined as follows:

1. Extracted and abstracted data flow into the study-specific database and are combined by relying on a common patient identifier.
2. Derived data variables and tables are created by applying defined algorithms that combine structured and/or abstracted data. For example, LOTs are derived using disease-specific deterministic rules, and this data can then be used for cohort selection for studies based on a specific treatment line. Drug episodes are also derived to facilitate analyses related to treatment span, such as duration of treatment or time to treatment discontinuation.
3. The combined dataset is de-identified and used in research deliverables.

A.3 Data Quality Assurance and Quality Checks

RWD is considered fit-for-purpose when it is of sufficient quality as well as relevant, robust, and representative within a given clinical and regulatory context. Maintaining data quality dimensions, such as accuracy, reliability, relevance, and completeness, is a continual, dynamic process throughout the study.

QA/QC oversight activities for real-world dataset(s) are conducted during the course of a study following documented business processes and procedures. At a high level, QA/QC oversight activities for curating real-world datasets can be grouped into the following areas:

- **Operational and process oversight:** Documented standard operating procedures allow **Redacted** Health to consistently complete study-related activities, anticipate potential risks, increase efficiency, and facilitate planning. Examples of operational processes are described below:
 - Structured data are extracted and harmonized in accordance with defined processes.
 - Structured data are extracted from source EHR systems from the site of clinical care alongside other external data (e.g., mortality data sources), in accordance with defined business processes to ensure secure and timely extracts.
 - Harmonization of structured data across data sources is done to standardize coding and/or terminology without changing the original meaning and context of the data. Defined harmonization processes are used and reviewed periodically to ensure they are up to date and consistent with source data, use cases, and standards.
 - Unstructured data is abstracted using controlled abstraction forms and in accordance with specific defined procedures.
 - Controlled abstraction forms are developed for abstractors to consistently abstract unstructured data in accordance with written instructions.
 - Data are derived by applying established deterministic rules to multiple data components.
 - Deterministic rules are developed collaboratively by a cross-functional team, and the derived data that are the output of these rules are reviewed periodically.
- **Data quality oversight:** Activities are designed to provide oversight during the extraction, abstraction, and derivation of RWD to ensure that data are generated, documented, and reported according to **Redacted**'s processes. An overview of quality processes is described below:
 - Extraction
 - Quality oversight is provided using automated checks designed to monitor the extraction process and generate alerts should the extracted data be determined to be incomplete, inaccurate, or sufficiently out-of-date in comparison to the source data. Automated alerts for NLP-extracted data are designed to monitor the stability (e.g., stability of month-over-month predictions) and performance (e.g., performance of models as compared with expectations).
 - Harmonization
 - Quality checks are performed on processes governing structured data harmonization to ensure consistency in mapping per the established mapping guidelines.
 - Abstraction
 - Manual (i.e., human review) and technology-enabled (i.e., programmatic) data review and oversight of unstructured data is provided by a cross-functional team (e.g., oncology, statistical, clinical data, engineering).
 - Inter-rater agreement for a percentage of abstracted RWD variables (i.e., the same abstraction form for the same patient is processed by two different abstractors independently, and the result of the two different abstraction tasks is compared) is monitored and an investigation performed when an issue is identified.
 - Performance for artificial intelligence–derived variables used for cohort selection are continually monitored by comparing against a fully abstracted reference standard to ensure they are highly sensitive (e.g., greater than or equal to 95% sensitivity).
 - Derivation

- Automated pipeline tests on derived data code changes are conducted to verify acceptable output parameters are met according to specified requirements.
- **Systems oversight:** These processes are built into technical systems and/or workflows to provide programmatic oversight and efficiency. [Redacted] software is developed in accordance with Good Engineering Practices (GEP; International Society for Pharmaceutical Engineering, 2021) for each phase of the software development lifecycle. An overview of system processes is described below.
 - System changes logs/change control to ensure traceability
 - Each code change has a unique ID (e.g., tag) automatically generated by [Redacted]'s source code repository
 - Data provenance and traceability to source documentation
 - Source data elements are archived in [Redacted]'s Data Hosting Cloud Provider for a minimum of seven years
 - Transparency in data provenance with audit trails throughout the data lifecycle
 - The state of the codebase during final delivery (i.e., commit reference) is archived
 - Abstraction system ensures only trained staff complete abstraction
 - Software is developed in accordance with GEP, including defined review, testing, and oversight of electronic systems
 - [Redacted] GEP Guideline provides guidance for each phase of the software development lifecycle, which includes: Analyze, Design, Develop, Test, and Deploy

A.4 Reference for Systems Oversight

Bennett C, Block J, Drinan M, et.al. ISPE Good Practice Guide: Good Engineering Practice, 2nd Ed. International Society for Pharmaceutical Engineering, 2021fi.

A.5 ICD-9/ICD-10 codes used to identify CCI

CCI Condition	ICD-9	ICD-10
Myocardial infarction	410, 412	I21, I22, I252
Congestive heart failure	39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 428, 4254 - 4259	I099, I110, I130, I132, I255, I420, I43, I50, P290, I425 - I429
Peripheral vascular disease	0930, 440, 441, 4471, 5571, 5579, V434, 4431 - 4439	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Cerebrovascular disease	36234, 430 - 438	G45, G46, H340, I6
Dementia	290, 2941, 3312	F051, G30, G311, F00 - F03
Chronic pulmonary disease	4168, 4169, 5064, 5081, 5088, 490 - 505	I278, I279, J684, J701, J703, J40 - J47, J60 - J67
Rheumatic disease	4465, 7148, 725, 7100 - 7104, 7140 - 7142	M05, M06, M315, M32, M33, M34, M351, M353, M360
Peptic ulcer disease	531 - 534	K25 - K28

Mild chronic liver disease	07022, 07023, 07032, 07033, 07044, 07054, 0706, 0709, 570, 571, 5733, 5734, 5738, 5739, V427	B18, K709, K717, K73, K74, K760, K768, K769, Z944, K700 - K703, K713 - K715, K762 - K764
Moderate or severe chronic liver disease	4560 – 4562, 5722 - 5728	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767
Diabetes with chronic complications	2504, 2505, 2506, 2507	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E132, E133, E134, E135, E137
Diabetes without chronic complications	2500, 2501, 2502, 2503, 2508, 2509	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E130, E131, E136, E138, E139
Hemiplegia	3341, 342, 343, 3449, 3440 - 3446	G041, G114, G801, G802, G81, G82, G839, G830 - G834
Renal disease	40301, 40311, 40391, 40402, 40403, 40412, 40413, 40492, 40493, 582, 585, 586, 5880, V420, V451, V56, 5830 - 5837	I120, I131, N18, N19, N250, Z940, Z992, N032 - N037, N052 - N057, Z490 - Z492
HIV/AIDS	044	B20, B21, B22, B24

A.6 LOT Rules

1. THERAPIES ELIGIBLE FOR INCLUSION IN LINES OF THERAPY

- 1.1. Systemic treatment, as evidenced by an order or administration of an antineoplastic or steroid (IV dexamethasone, oral dexamethasone, and oral prednisone) recorded in the EHR, are included in lines of therapy (LOT) [rule implemented: 12/31/15, updated 9/30/19]
 - 1.1.1.A “drug episode” of systemic therapy is defined as an administration or a non-canceled order for non-abstracted therapies
- 1.2. Oral therapy information is captured from unstructured data and included in lines of therapy. Treatment with oral therapies is reported in spans, where treatment extends from a start date to a defined end date. Multiple treatment spans are reported for a specific oral therapy when that drug is stopped or held for at least 60 days and then restarted [rule implemented: 12/31/15]
- 1.3. All dates of bone marrow transplants, including both autologous and allogeneic transplants, are captured from unstructured data and are included in lines of therapy. The date of the transplant is defined as the date on which the transplanted cells are infused [rule implemented: 12/31/15]
- 1.4. Radiotherapy and surgery are not included in lines of therapy [rule implemented: 12/31/15]
- 1.5. IV/SC therapy information for selecting agents of interest is captured from unstructured data and included in lines of therapy. Treatment with IV/SC therapy coming from unstructured data is reported in spans, where treatment extends from a start date to a defined end date. Multiple treatment spans are reported for a drug

or drugs when that therapy is stopped or held for at least 60 days and then restarted [rule implemented: 11/30/23]

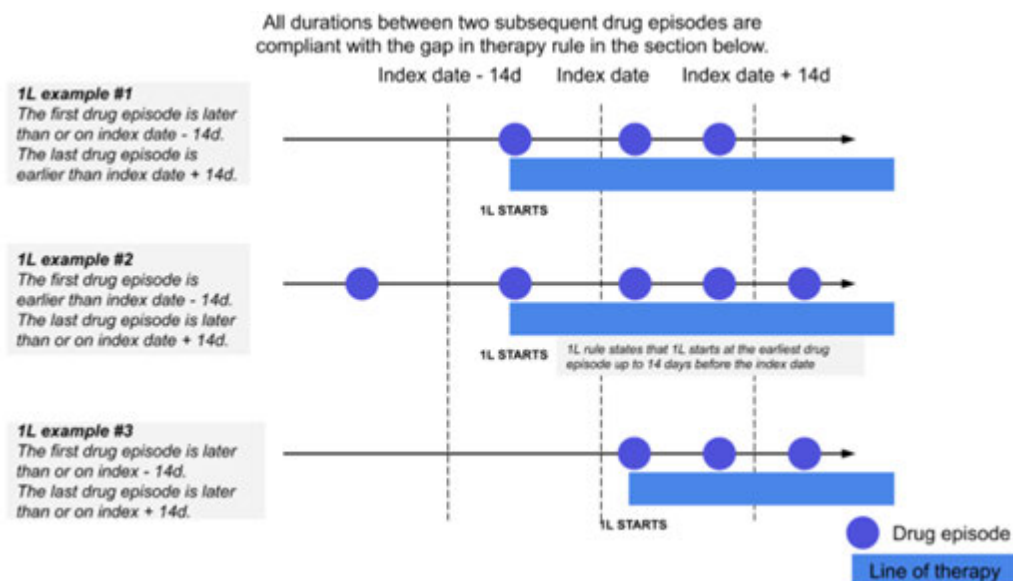
- 1.6. The following therapy is excluded from lines of therapy: mesna. [rule implemented: 12/31/16, updated 6/30/23]
- 1.7. Structured IV or SC orders that are contradicted by abstracted IV or SC data will not be considered in lines of therapy [rule implemented 11/30/23]
- 1.8. CAR-T cellular therapy infusion date is captured from unstructured data and included in lines of therapy [rule implemented: 4/29/22]
- 1.9. Therapies (including supportive agents, e.g., corticosteroids) given within 30 days post-CAR-T cellular therapy are excluded from lines of therapy [rule implemented: 4/29/22]
- 1.10. Structured IV or SC orders will not be considered in lines of therapy [rule implemented 4/30/25]

2. INDEX DATE

- 2.1. The index date is defined as the patient's date of diagnosis with MM, as identified from unstructured data [rule implemented: 12/31/15]

3. START OF FIRST LOT (1L)

- 3.1. The start of the 1L is defined as the date of first drug episode of an eligible therapy that is given after or up to 14 days before the index date, and after the start of structured activity (earliest structured visit or therapy). Only an abstracted oral or an abstracted IV or SC therapy can start 1L before the start of structured activity [rule implemented: 12/31/15, updated: 11/30/23]



- 3.2. Transplants are not eligible to be the start of the 1L. For cases where a transplant appears as the first treatment after the index date and start of structured activity, the transplant is marked as Line Zero (as noted below) [rule implemented: 06/30/17]
- 3.3. LINE ZERO: To indicate patients for whom, therapy data may be missing, Line Zero is created in patients whose start of MM treatment (as captured through unstructured data) is more than 30 days before the start of structured activity. In these patients, Line Zero extends from the start of MM treatment to the start of structured activity [rule implemented: 12/31/15]
 - 3.3.1. Line Zero does not contain information on specific therapies
 - 3.3.2. Note: For some patients, Line Zero will extend beyond the patient's start of structured activity. Line Zero contains all treatments that occurred before the start of structured treatment
 - 3.3.3. Note: For some patients, Line Zero will be named Transplant if the transplant would otherwise have been the start of their 1L. These patients likely had other therapy prior to their start of structured activity

4. DEFINITION OF A LOT

- 4.1. The definition of a LOT is generally the first eligible drug episode plus other eligible drugs given within 28 days. The name of the "regimen" for that LOT is the combination of therapies in that line, unless otherwise noted [rule implemented: 12/31/15; amended [12/31/2016]
- 4.2. The LOT allows for three days of overlap between abstracted agents (oral, IV, or subcutaneous) and any other drug without rolling them up into a single line [rule implemented: 9/30/17; updated 11/30/23]
 - 4.2.1. For example, if abstractors report that a patient stopped lenalidomide on 10/6 and initiated pomalidomide on 10/4, the stop date of lenalidomide will be backdated to 10/3 and the two agents will be reported as distinct monotherapy lines
- 4.3. CAR-T cellular therapy infusions always advance a LOT. Any treatments started within 14 days before CAR-T cell infusion as part of a conditioning regimen are ineligible for LOT [rule implemented: 4/29/22]

5. MAINTENANCE

- 5.1. Bortezomib, lenalidomide, thalidomide, daratumumab, daratumumab/hyaluronidase-fihj (daratumumab and daratumumab/hyaluronidase-fihj are considered equivalent), and ixazomib are eligible to be considered maintenance therapy. Maintenance therapy does not advance the line number and can also apply to Line Zero. It is considered maintenance when one of these drugs is used as monotherapy and meets one of the following criteria: [rule implemented: 12/31/15, updated 9/30/2019, updated 7/31/20; updated 10/31/21; updated 6/30/23]:
 - 5.1.1. Monotherapy duration more than 60 days (allowing for stops/starts of abstracted oral spans without addition of other treatments) follows a combination therapy that lasts more than 30 days (monotherapy start date

must be within 180 days of the end of combination) [rule amended 8/30/2022]

- 5.1.1.1. For patients receiving daratumumab or daratumumab/hyaluronidase-fihj, in order for it to qualify as maintenance, the combination therapy must also include daratumumab or daratumumab/hyaluronidase-fihj [rule added 6/30/2023]

OR

- 5.2. Monotherapy (with no minimum duration requirement) follows transplant by less than 365 days with no interim antineoplastic treatment [rule amended 8/30/2022]

- 5.2.1. Pomalidomide, thalidomide, and lenalidomide are eligible to be considered maintenance therapy when given with: [rule implemented 6/30/25]

- 5.2.1.1. Carfilzomib OR bortezomib OR ixazomib

- 5.2.1.2. Isatuximab-irfc OR daratumumab OR daratumumab/hyaluronidase-fihj

6. GAP IN THERAPY

N/A

7. CHANGES PERMITTED WITHIN A LOT

- 7.1. When an abstracted transplant date occurs during a line, the transplant does not advance the LOT. The name “transplant” is assigned to the portion of the line starting on the transplant date and ending at either initiation of post-transplant maintenance or the start of the subsequent line. Any structured treatment or abstracted therapy (oral, IV, or subcutaneous) given between seven days prior to and 30 days after the transplant date are ineligible for LOT [rule implemented: 12/31/15; rule last updated 11/30/23]
- 7.2. For the following substitutions, the line will be named according to the drug given for the longest duration within the line:
 - 7.2.1. Substitution of dexamethasone for prednisone and vice versa does not advance the LOT [rule implemented: 12/31/15]
 - 7.2.2. Substitution of rituximab for rituximab/hyaluronidase and vice versa does not advance the LOT [rule implemented: 9/30/19]
 - 7.2.3. Substitution of daratumumab for daratumumab/hyaluronidase and vice versa does not advance the LOT [rule implemented: 07/31/20]
 - 7.2.4. Substitution of the reference product for a biosimilar or vice versa does not advance the LOT (e.g, trastuzumab and trastuzumab-anns) [rule implemented: 8/28/20]
- 7.3. The addition of an *imid drug within the first 90 days of a regimen that had not previously contained an *imid does not advance the LOT (*imids = lenalidomide, pomalidomide, thalidomide). Note: the drugs in the initial regimen must overlap with this *imid drug for this rule to be applied [rule implemented: 12/31/2016]

- 7.4. The addition of a proteasome inhibitor within the first 90 days of a regimen that had not previously contained a proteasome inhibitor does not advance the LOT (proteasome inhibitor drugs = bortezomib, carfilzomib, or ixazomib) Note: the drugs in the initial regimen must overlap with this proteasome inhibitor for this rule to be applied [rule implemented: 12/31/2016]
- 7.5. The addition of lenalidomide in 1L to a line that already contained cyclophosphamide does not advance the LOT and cyclophosphamide is removed from the LOT name. Note: this switch must occur within 60 days of line start for this rule to be applied [rule implemented: 6/30/22]
- 7.6. Resuming the same regimen after transplant that was previously administered immediately prior to transplant does not advance the line and will be labeled as a consolidation phase. The presence of a Clinical Study Drug will not impact the rule [rule implemented: 3/31/25]

8. CHANGES NOT PERMITTED WITHIN A LOT

N/A

9. LOT END DATE

- 9.1. For the most recent LOT, the LOT end date is defined as:
 - 9.1.1.[For patients with no recorded date of death] the date of last patient-level confirmed activity (i.e., the last record of patient vitals, medication administrations, reported laboratory tests/results, or abstracted oral episode).
 - 9.1.2.[For patients with a recorded date of death] the earlier date of the date of death and the last patient-level confirmed activity (i.e., the last record of patient vitals, medication administrations, reported laboratory tests/results, or abstracted oral episode) (Note that for patient privacy and de-identification purposes, date of death is generalized to the last day of the month of death).
 - 9.1.3. When available, the abstracted end date for an abstracted treatment span is used as the LOT end date instead of its corresponding structured order
- 9.2. For all other lines, the end date is the day before the start date of the next LOT

10. INTERNATIONAL MARKET CONSIDERATIONS (UK, Germany, and Japan)

- 10.1. Cyclophosphamide administered only once within the year prior to transplant is excluded from Lines of Therapy.

Steroids (dexamethasone, prednisone, prednisolone, methylprednisolone) do not advance a LOT.

A.7 Mortality Additional Information

Redacted has developed a mortality variable that amalgamates internal and external data sources to generate a consensus representation of our best understanding of a patient's vital status and date of death. This enables our data to support outcomes research questions that require an understanding of survival of cancer patients in the real world.

Mortality data comprises several concepts, including: (1) Vital status (whether the patient is known to be deceased); (2) Date of death; and (3) Cause of death. We currently incorporate information on the first two of these concepts for all patients in our data offerings. When the “date of death” variable (a.k.a., “*DateofDeath*” in the data dictionary) is available (i.e., a date is present), this signals that the vital status is “deceased” although there is not a separate variable in the dataset delineating vital status. When the date of death variable is not available or missing, this signals that the vital status is “presumed alive.” Cause of death is not available at this time in **Redacted** data.

Redacted curates mortality information from electronic health record (EHR) sources to which we have access. This includes the patient’s date of death as entered into a structured field in the EHR as well as information captured in unstructured documents such as clinician notes and condolence letters. Additionally, the EHR data is linked with external death data sources to add in dates of death that might be missing from the EHR.

In order to determine the optimal external death data source(s), we evaluated options on the basis of completeness, accuracy and recency. Based upon this review, we have selected to combine two sources outside the EHR: the SSDI, and a source that mines data from obituaries, funeral homes and other sources. We employ a deterministic matching algorithm to link these datasets to our patient-level data. We also remove any dates that are known to be incorrect (for instance, death dates that occur before abstracted diagnosis dates), as well as those required to be removed for de-identification reasons, specifically when a date of death occurs in the same month as the patient’s clinical eligibility date.

Date of death is a consensus variable across the three data sources (EHR, SSDI and obituary data). We generate the variable according to the following rules and hierarchy (preference is based on comparative analyses with the National Death Index as the gold standard):

1. Use abstracted dates over structured dates when the abstracted date granularity is at the day level.
 2. Use the following rules when there are multiple structured dates of death:
 1. SSDI
 2. Obituary data
 3. EHR
- If all three dates are in agreement, that date of death is selected
 - If any two dates are in agreement, that date of death is selected
 - If none of the dates are in agreement, then the rank order to which the date of death is selected is:

Document Approval Record

Redacted		

Document Approval Record

Document Name:

C1071050_Protocol_Pfizer-Flatiron_v2.0_22May2026

Document Title:

C1071050_Protocol_Pfizer-Flatiron_v2.0_22May2026

Signed By:

Date(GMT)

Signing Capacity

Rubino, Heather

23-Jun-2026 12:40:01

Final Approval